BLOCKING THE MIGRATION OR METASTASIS OF CANCER CELLS BY AFFECTING ADHESION PROTEINS AND THE USES OF NEW COMPOUNDS THEREOF

This application claims priority of PCT/US2007/077273, filed August 30, 2007, U.S. Serial No. 60/890,380, filed on February 16, 2007, U.S. No. 60/947,705, filed on July 3, 2007, and U.S. Serial No.11/683,198, filed on March 7, 2007, which claims benefit of U.S. Serial Nos. 60/795,417, filed on April 27, 2006, 60/841,727, filed on September 1, 2006, 60/890,380, filed on February 16, 2007, and International Application No. PCT/US2006/016158, filed April 27, 2006, which claims the benefit of the priority of the following applications: (1) U.S. Serial Nos. 11/289142, filed November 28, 2005, and 11/267,523, filed November 4, 2005; (2) International Application No. PCT/US05/31900, filed September 7, 2005 (which claims the priority of U.S. Serial Nos. 60/617,379, filed October 8, 2004, 60/613,811, filed September 27, 2004, and 60/607,858, filed September 7, 2004); (3) U.S. Serial No. 11/131,551, filed May 17, 2005; and (4) U.S. Serial No. 11/117,760, filed April 27, 2005. The contents of these preceding applications are hereby incorporated in their entireties by reference into this application.

FIELD OF THE INVENTION

This invention provides methods and compositions for affecting the gene expression in cells as a result that cure diseases, wherein the methods comprise reducing the syndrome of diseases. In an embodiment the method comprise inhibition of gene expression. In an embodiment the method comprises stimulating the gene expression.

This invention provides methods, processes, compounds and compositions for modulating the gene expression or secretion of adhesion proteins or their receptors to cure disease, wherein the modulating comprises positive and negative regulating; wherein comprises inhibiting cancer growth, wherein the adhesion proteins or receptors comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK.

BACKGROUND OF THE INVENTION

Metastasis is the late stage of cancer in which cancer cells leave the original tumor site and migrate to other parts of the body. The cancer cells break away from the primary tumor and attach to the surrounding extracellular matrix and migrate to other parts of the body via bloodstream or the lymphatic system. The adhesion protein play an essential role in cancer metastasis.

When metastasis occurs, there are numbers of way with which it can be treated, including radiosurgery, chemotherapy, radiation therapy, biological therapy hormone therapy, surgery and laser-immunotherapy. However, these are often not able to prevent the genesis of metastatic cancer.

SUMMARY OF THE INVENTION

This invention provides a method of modulating the adhesion of cancer cell and block their migration, metastasis or inhibit the growth of cancers or anti-angiogenesis, wherein the adhesion protein and their receptors comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK.

This invention provides a method of reducing the adhesion protein in cell and block the migration, metastasis of cancer cells or inhibit the growth of cancers or anti-angiogenesis, wherein the adhesion proteins or its receptors comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, this invention provides a method of reducing the secretion of fibronectin. In an embodiment, this invention provides a method for inhibiting the expression of adhesion proteins, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. This invention provides a method of inhibiting the growth, migration, metastasis of cancer by altering the characteristics of membrane of cancer cells, wherein the characteristics comprise adhesion protein; wherein the cancers comprise breast, leukocyte, liver, ovarian, bladder, prostate, skin, bone, brain, leukemia, lung, colon, CNS, melanoma, renal and cervix cancer.

DETAILED DESCRIPTION OF THE FIGURES

Figure 1: Time studies of inhibition of Fibronectin secretion from cancer cells (ES2) after incubation of Xanifolia-Y. Fibronectin released in culture medium was determined byWestern blot A: (results of experiment F1) Y is Xanifolia compound Y; B: (results of experiment F3); C: (results of experiment F4)

Figure 2: Inhibition of Fibronectin Secretion by Xanifolia-Y (Western Blot).
A: result of experiment F5; B: result of experiment F7; C: result of experiment F8; D: result of experiment F11; E: result of experiment F12; F: result of experiment F13; G: result of experiment F14B; H: result of experiment 14C

Figure 3: Inhibition of Fibronectin Secretion by Xanifolia-Y (Western Blot).
A: result of experiment F23; B: result of experiment F24; C: result of experiment F26; D: result of experiment F27; E: result of experiment F29; F: result of experiment F28.

Figure 4: Inhibition of Fibronectin Secretion by Xanifolia-Y (Western Blot).
A: result of experiment F30; B: result of experiment F31; C: result of experiment F32;D: result of experiment F33A; E: result of experiment F20.

Figure 5: Increase synthesis of Angiopoietin-2 in ES2 cells by Xanifolia-Y treatment.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides methods and compositions for modulating the gene expression to cure diseases or reduce the syndrome of diseases, wherein the modulating comprises positive and negative regulating. In an embodiment, the method comprises inhibiting the gene expression. In an embodiment the method comprises stimulating the gene expression.

This invention provides methods and compositions for inhibiting the migration, metastasis or growth of cancers or anti-angiogenesis, wherein the methods comprise affecting the gene expression, wherein comprise affecting the adhesion proteins or their receptors, reducing adhesion protien, or inhibiting the expression or secretion of adhesion proteins, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK.

This invention provides methods and compositions for inhibiting the migration, metastasis or growth of cancers or anti-angiogenesis, wherein the methods comprise affecting the gene expression, wherein comprises stimulating the gene expression.

This invention provides a method for altering the characteristic of cancer cell membrane resulting in blocking the migration, metastasis of cancer cells or inhibit the growth of cancers or anti-angiogenesis, wherein the method comprises reducing adhesion protiens or their receptors, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK.

This invention provides methods, processes, compounds and compositions of reducing adhesion protein of cells, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, methods comprise inhibiting the gene expression. In an embodiment, this invention provides a method of reducing the secretion of fibronectin. In an embodiment the method can block the migration, metastasis of

cancer cells or inhibit the growth of cancers or anti-angiogenesis, wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer,

This invention provides a method of altering the characteristic of cancer cell membrane, wherein the method comprises altering the secretion of adhesion proteins, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, the methods, processes, compounds and compositions comprises blocking, suppressing or inhibiting the expression or secretion of adhesion protein, wherein the adhesion proteins . In an embodiment, the methods, processes, compounds and compositions is interacting with adhesion protein, wherein the adhesion proteins. In an embodiment the methods, processes, compounds or compositions can block the migration, metastasis of cancer cells or inhibit the growth of cancers or anti-angiogenesis, wherein the cancers comprise breast, leukocyte, liver, ovarian, bladder, prostate, skin, bone, brain, leukemia, lung, colon, CNS, melanoma, renal and cervix cancer.

The adhesion proteins help cancer cell adhesion, invasion or metastasis, wherein the cancers comprise ovarian cancer. Reducing the adhesion proteins will reduces the metastasis of cancers.The fibronectin is one of the key factors in the biology of epithelial ovarian cancers. The reducing of fibronectin will inhibit the metastasis of cancer cells.

This invention provides a method and composition for inhibiting the secretion of adhesion protein comprising fibronectin in order to cure the diseases, wherein the diseases comprise inhibiting cancer growth, wherein the cancers comprise breast, leukocyte, liver, ovarian, bladder, prostate, skin, bone, brain, leukemia, lung, colon, CNS, melanoma, renal and cervix cancer.

This invention provides a composition for inhibiting the growth, migration, metastasis of cancer and by altering the characteristics of membrane of cancer cell, wherein the characteristics comprise adhesion of proteins; wherein comprising the secretion of

proteins or the adhesion of cells; wherein the characteristic comprise adhesion ability; wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK; wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer; wherein the method is administering contacting XanifoliaY0, Y1, Y2, Y, Y7, Y8, Y9, Y10, ACH-Y or a salt, ester, metabolite thereof. In an embodiment the composition is the compound selected from formulas in this application.

This invention provides a method for altering the adhesion characteristic of membrane of cancer cell, wherein the method compring reducing the adhesion ability, wherein the method comprises reducing the secretion of fibronectin. wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer, wherein the method is administering contacting an effective amount of Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10, ACH-Y or a salt, ester, metabolite thereof. In an embodiment, the method is administering contacting an effectie amount of the compound selected from formulas in this application. In an embodiment, the method is inhibiting the growth, migration, metastasis of cancer. In an embodiment the compound may be selected from formula (1A), (1B), (1C) and (1D). In an embodiment, the compound comprises a triterpene backbone, two angeloyl groups and sugar moiety. In an embodiment the compound(s) are selected from Xanifolia (x), Escin or Aescin. In an embodiment the compound(s) are selected from Compound A to X and A1 to X1. In an embodiment the compound(s) are selected from Compound Z1 to Z7, in the application.

This invention provides a composition for inhibiting the growth, migration, metastasis of cancer by altering the adhesion characteristic of membrane of cancer cell, wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer.

This invention provides a method and composition for reducing of adhesion protein to cure the diseases, wherein the diseases comprise inhibiting cancer growth, reducing leg swelling, symptoms of chronic venous insufficiency, peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, expectorant, peripheral vascular disorders, cerebro-organic convulsion, cerebral circulation disorder, cerebral edema, psychoses, dysmenorrheal, hemorrhoids, episiotomies, peripheral edema formation or postoperative swelling; for reducing symptoms of leg pain; for treating pruritis, lower leg volume, for reducing symptoms of pain; thrombosis, thromophlebitis; for preventing gastric ulcers antispasmotic, comprising administering to a subject, in need thereof, an effective amount of the composition of this invention.

In an embodiment, the method comprises interacting with adhesion protien, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, this invention provides a method of reducing the secretion of fibronectin.

In an embodiment, the method comprises reducing the adhesion ability of adhesion protein; wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK.

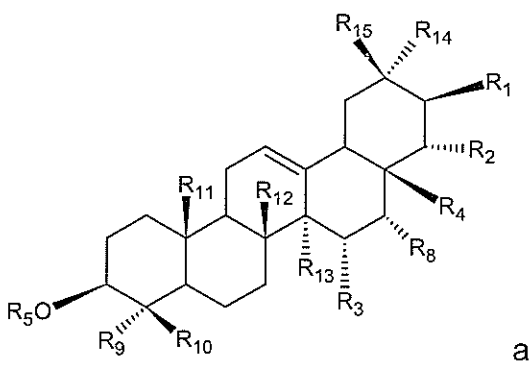
In an embodiment, the method comprises modulating the secretion of adhesion protien, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, the method comprises blocking the secretion of adhesion protien, wherein the adhesion protein comprising fibronectin. In an embodiment the method is administering contacting an effective amount of the compound selected from formulas in this application.

In an embodiment the method is administering contacting an effective amount of the compound in this application comprising Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10,

ACH-Y, Xanifolia (x), Escin or Aescin or a salt, ester, metabolite thereof. In an embodiment the compound(s) are selected from Compound A to X and A1 to X1. In an embodiment the compound(s) are selected from Compound Z1 to Z7, in the application. In an embodiment the compound may be selected from formula (1A), (1B), (1C) and (1D).

This invention provides a method and composition for altering the characteristic of adhesion protein to cure diseases, wherein the characteristic comprising adhesion ability, wherein the method comprises reducing the secretion of fibronectin, wherein the diseases comprise inhibiting cancer growth, reducing leg swelling, symptoms of chronic venous insufficiency, peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, expectorant, peripheral vascular disorders, cerebro-organic convulsion, cerebral circulation disorder, cerebral edema, psychoses, dysmenorrheal, hemorrhoids, episiotomies, peripheral edema formation or postoperative swelling; for reducing symptoms of leg pain; for treating pruritis, lower leg volume, for reducing symptoms of pain; thrombosis, thromophlebitis; for preventing gastric ulcers antispasmotic, comprising administering to a subject, in need thereof, an effective amount of the composition of this invention; wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK In an embodiment the method is administering contacting an effective amount in a subject with the compound selected from formulas in this application.

A isolated, purified or synthesized compound or its salt, ester, metabolite or derivative thereof, having the formula of



also named (1A),

wherein

R1 is selected from hydrogen, hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted O-alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof;

R2 is selected from hydrogen, hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted O-alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof;

R4 represents CH_2R6 or COR6, wherein R6 is selected from a group consisting of hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted O-alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof;

R3 is H or OH;

R8 is H or OH, particularly OH;

R5 is a hydrogen or sugar moiety(ies), wherein the sugar moiety(ies) is/are selected from a group consisting of glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, and derivatives or combination thereof; wherein R9, R10, R11, R12, R13, R14, R15 are independently attached a group selecting from CH_3, CH_2OH, CHO, COOH, COO-alkyl, COO-aryl, COO-heterocyclic, COO-heteroaryl, CH_2Oaryl, CH_2O- heterocyclic, CH_2O- heteroaryl, alkyls group, hydroxyl, acetyl group, particularly CH_3;

wherein at least two of R1, R2 and R6 are compriseing a group selected from O-angeloyl, O-tigloyl, O-senecioyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted O-alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof; or at least one of R1, R2, and R4 is a sugar moiety substituted with at least two groups selected from a group consisting of angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, and a derivative thereof; or

wherein R4 is CH_2R6; wherein R1 and R2 independently consists an O-angeloyl group, or at least two of R1, R2 and R6 are O-angeloyl or at least one of R1, R2 or R6 is a sugar moiety with two O-angeloyls;

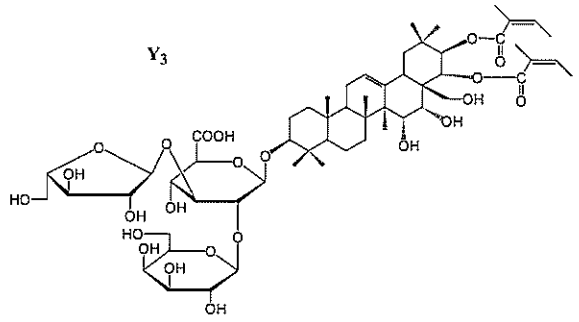
wherein R5 is/are the sugar moiety(ies) selected from the following sugars and alduronis acids: glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose,

fructose, glucuronic acid, galacturonic acid; or their derivatives thereof, or the combination thereof; wherein the sugar preferably comprises glucuronic acid, arabinose and galactose.

In an embodiment,wherein R5 is/are sugar moiety(ies) selected from a group consisting of glucose, galactose, arabinose, alduronic acid, glucuronic acid, galacturonic acid, and a derivative or combination thereof;

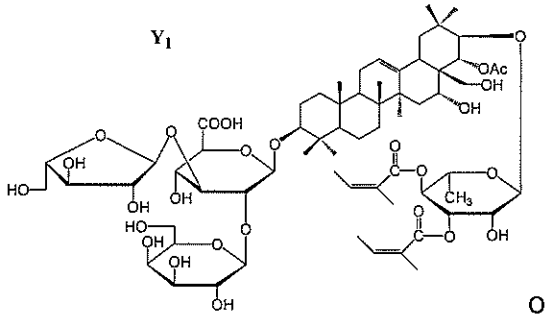
In an embodiment the method is administering contacting the compounds, wherein the compound is selected from the following:

a) An isolated, purified or synthesized compound is having structure Xanifolia(Y),



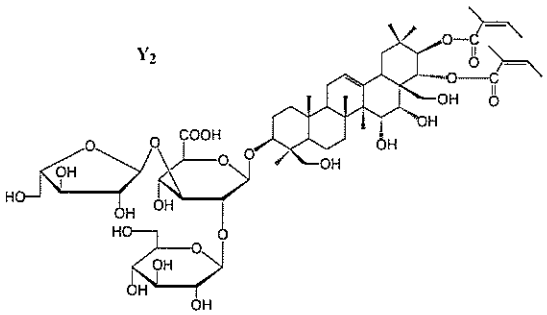
or chemical name: 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosy (1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene;

b) An isolated, purified or synthesized compound is having structure Xanifolia (Y1),



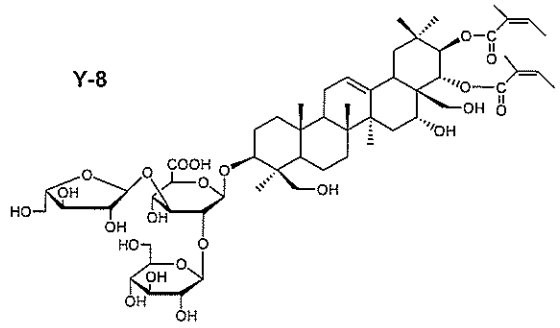
or chemical name: 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3,4-diangeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene;

c) An isolated, purified or synthesized compound is having structure Xanifolia (Y2),



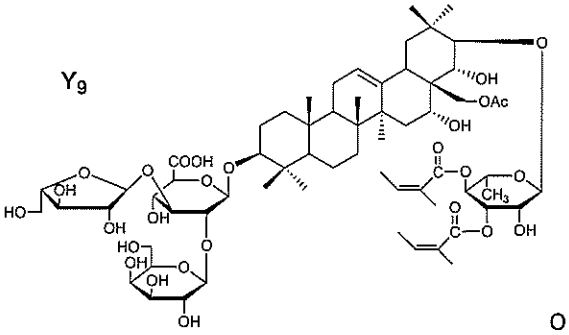
or chemical name: 3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosy (1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 24β, 28-heptahydroxyolean-12-ene;

d) An isolated, purified or synthesized compound is having structure Xanifolia (Y8),



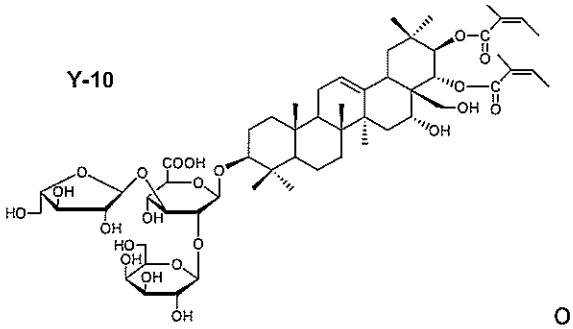
or chemical name: 3-*O*-[*β*-glucopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 24*β*, 28-hexahydroxyolean-12-ene;

e) An isolated, purified or synthesized compound is having structure Xanifolia (Y9),



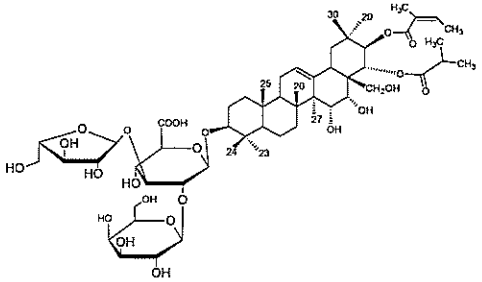
or chemical name: 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*-(3,4-diangeloyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene; and

f) An isolated, purified or synthesized compound is having structure Xanifolia (Y10),



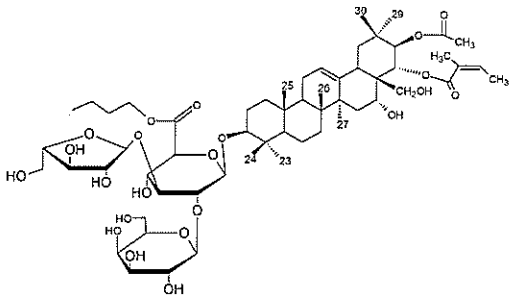
or chemical name: 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene.

g) An isolated, purified or synthesized compound is having structure Xanifolia (Y0),



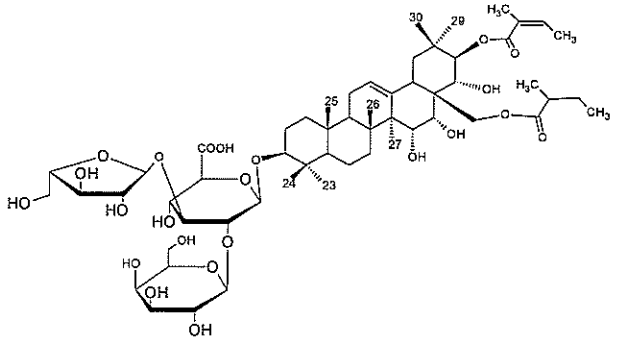
or chemical name: 3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-angeloyl, 22-O-(2-methylpropanoyl)-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

h) An isolated, purified or synthesized compound is having structure Xanifolia (X),



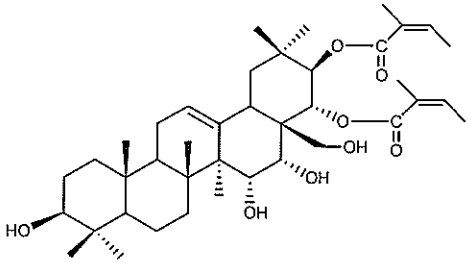
or chemical name: 3-*O*-{[*β*-D-galactopyranosyl (1→2)]-[*α*-L-arabinofuranosyl (1→3)]-*β*-D-glucuronopyranoside butyl ester}-21-*O*-acetyl-22-*O*-angeloyl- 3*β*,16*α*,21*β*,22*α*,28-pentahydroxyolean-12-ene.

i) An isolated, purified or synthesized compound is having structure (Y7),



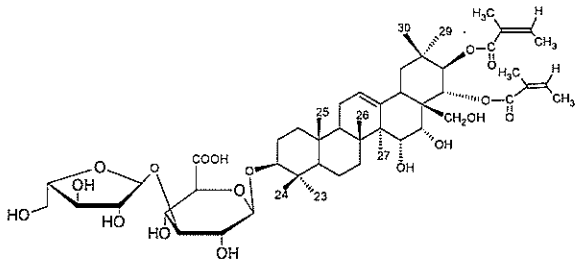
or chemical name: 3-*O*-[*β*-D-galactopyranosyl-(1→2)]-*α*-L-arabinofuranosyl-(1→3)-*β*-D--glucuronopyranosyl-21-*O*-angeloyl-28-*O*-2-methylbutanoyl-3*β*, 15 *α*, 16*α*, 21*β*, 22*α*, 28-hexahydroxyolean-12-ene

j) An isolated, purified or synthesized compound is having structure (ACH-Y):

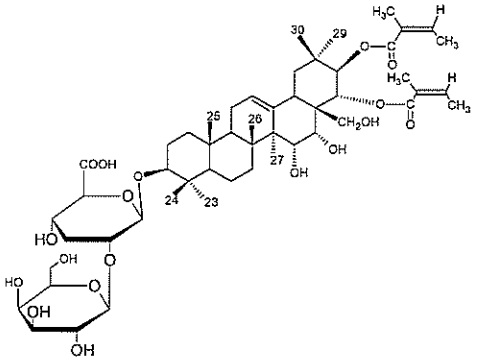


In an embodiment the method is administering contacting the compound, wherein the compound is selected from the following:

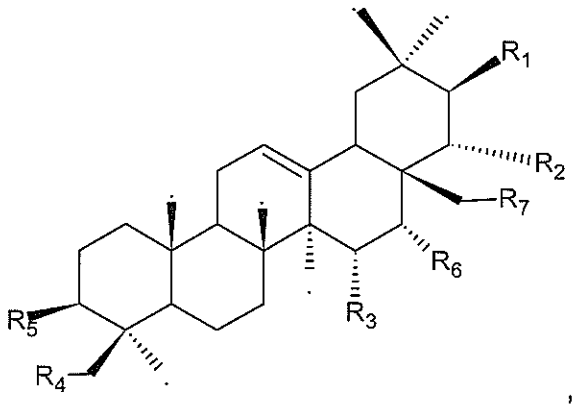
k) An isolated, purified or synthesized compound is having a structure:



l) An isolated, purified or synthesized compound is having a structure:



In an embodiment the method is administering contacting the compound, wherein the compound is isolated, purified or synthesized having a structure selected from following formulas:



, (1C)

wherein R1, R2 are individually selected of an O-acetyl or O-angeloyl; wherein the R3, R4, R5, R6, R7 is hydrogen or hydroxyl

In an embodiment the method is administering contacting the compound in this application comprising Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10, Xanifolia (x), Escin or Aescin or a salt, ester, metabolite thereof. In an embodiment the compound may be selected from formulas (1A), (1B), (1C) and (1D). In an embodiment, the

compound comprises a triterpene backbone, two angeloyl groups and sugar moiety. In an embodiment the compound(s) are selected from Xanifolia (Y0, Y1, Y2, Y, Y7, Y8, Y9, and Y10). In an embodiment the compound(s) are selected from Xanifolia (x), Escin or Aescin. In an embodiment the compound(s) are selected from Compound A to X and A1 to X1 in the application. In an embodiment the compound(s) are selected from Compound Z1 to Z7 in the application. In an embodiment the method is administering contacting the compound comprise of a triterpene wherein the carbon position 21, 21 has a unsaturated group and sugar moieties at carbon 3.

In an embodiment, compounds of this application reducing the adhesion ability inhibit bacteria in colonization and regulate tropism of cells.

In an embodiment, reducing the adhesion ability of cell or viruses in order to inhibit viruses binding to host cells, wherein the virus comprise HIV

The composition comprises the bioactive compounds from natural plants or synthesis.

The majority of the plants are from the Sapindaceae family, which has 140-150 genera with 1400-2000 species. The program is based on our purification methods and biological assays including the MTT assay See International Application No. PCT/US05/31900, filed September 7, 2005, U.S. Serial No. 11/289142, filed November 28, 2005, and U.S. Serial No. 11/131551, filed May 17, 2005, the contents of which are incorporated herein by reference

This invention provides the method uses of compositions comprising a triterpenoidal saponin. In an embodiment, the saponin has triterpenoid, triterpenoidal or other sapogenin, one or more sugar moieties and two angeloyl groups, or at least two side groups selected from the following groups: angeloyl groups, tigloyl groups or senecioyl groups, wherein the side groups are attached to the sapogenin backbone at carbon 21 and 22. In an embodiment, at least two of angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic or heteroraryl attached to the side groups; wherein the sugar moiety in the saponin comprises at least one or more of the following sugars and alduronis acids: glucose, galactose, rhamnose, arabinose, xylose, fucose,

allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, glucuronic acid, galacturonic acid; or their derivatives thereof, or the combination thereof; wherein the sugar preferably comprises glucuronic acid, arabinose and galactose.

This invention further provides a composition comprising the structures substituted with at least two side groups selected from angeloyl, tigloyl or senecioyl groups, wherein the side groups are attached to a triterpenoidal, triterpenoid, triterpenoidal or other sapongenin backbone. These structures are obtainable from the natural or synthesis.

This invention provides a method of preparing the bioactive compounds, comprising the steps of:

(a) Extracting roots, kernels, leaves, bark, stem, husks, seeds, seed shells or fruits of the plant, or combinations thereof with organic solvents such as ethanol or methanol to obtain an organic extract; (b) Collecting the organic extracts; (c) Refluxing the organic extract to obtain a second extract; (d) Removing the organic solvent from the second extract to obtain a third extract; (e) Drying and sterilizing the third extract to obtain a crude extract powder; (f) Fractionating the crude extract powder into fractions or components. Fractionation may be achieved by HPLC and FPLC chromatography with silica gel, C18 or other equivalent solid phase materials; (g) Monitoring the fractionating, if using HPLC or FPLC, the absorption wavelength at 207nm to 500nm may be used; (h) Identifying the bioactive components of the crude extract; (i) Purifying one or more bioactive components of the crude extract with FPLC to obtain one or more fractions of the bioactive component; and (j) isolating the bioactive components with chromatographic techniques that employ preparative columns and HPLC.

In an embodiment, this invention provides the method of MTT Assay TEST PLATFORM to test the bioactivities of the saponins or other compounds.

Cells. Human cancer cell lines were obtained from American Type Culture Collection: HTB-9 (bladder), HeLa-S3 (cervix), DU145 (prostate), H460 (lung), MCF-7 (breast), K562 (leukocytes), HCT116 (colon), HepG2 (liver), U2OS (bone), T98G (brain), SK-MEL-5 (Skin) and OVCAR-3 (ovary). The cells were grown in following culture media: HeLa-S3, DU145, MCF-7, Hep-G2 and T98G are in MEN (Earle's

salts); HTB-9, H460, K562 and OVCAR-3 in RPMI-1640; HCT-116 and U2OS in McCoy-5A. They are supplemented with 10% fetal calf serum, glutamine and antibiotics, and incubated in an incubator with 5% CO_2 humidified at 37°C.

MTT Assay. The procedure for MTT assay followed the method described by Carmichael et al. (1987) with modifications. The cells were seeded into a 96-well plate at concentration of 10,000/well for HTB-9, HeLa, H460, HCT116, T98G and OVCAR-3), 15,000/well for DU145, MCF-7, HepG2 and U2OS), and 40,000/well for K562 for 24 hours before drug-treatment. The cells were then exposed to the drugs for 48 hours (72 hours for HepG2 and U2OS, and 96 hours for MCF-7). After the drug-treatment, MTT (0.5 mg/mL) was added to cultures and incubated for an hour. The formazan (product of the reduction of tetrazolium by viable cells) formed and was dissolved with DMSO and the O.D. at 490nm, and was measured by an ELISA reader. The MTT level of the cells before drug-treatment was also measured (T0). The % cell-growth (%G) is calculated as: %G = (TD-T0 / TC-T0) x 100(1), where TC or TD represents O.D. readings of control or drug-treated cells.

When T0 > TD, then the cytotoxicity (LC) expressed as % of the control is calculated as: %LC = (TD-T0 / T0) x 100(2).

Micro Array: Analysis of gene expression of ES2 cells after Y-treatment by Microarray

In this invention, the microarray experiments were done in studying the gene expression. Total number of 54676 genes has been studied.

Cell culture and drug-treatment. ES2 cells were seeded in a T-25 flask with 4.5 million cells per flask for 24 hours. Cell culture was replaced with fresh medium with xanifolia-Y (Y) or DMSO no-drug -control (D) for 24 hours. Cells were then harvested for RNA isolation. Three experiments were done.

RNA extraction, labeling, hybridization, and data analysis. RNA was extracted from tumor cells using the Qiagen RNeasy Kit. RNA quality and quantity was checked by the Agilent BioAnalyzer and the NanoDrop® ND-1000 spectrophotometer respectively before further manipulation. The first and second cDNA strands were synthesized from 20 ng of total RNA using the Affymetrix T7 oligo(dT) primer protocol and kit for the two-cycle amplificaton. To produce amplified biotin-labeled-

cRNA, the cDNA was reverse transcribed by in vitro transcription using the MegaScript kit from Ambion. 15.0 µg of the labeled cRNA was fragmented and re-checked for concentration using the NanoDrop® ND-1000 spectrophotometer. A hybridization cocktail containing Affymetrix spike-in controls and fragmented labeled cRNA was loaded onto the Human U133 Plus 2.0 GeneChip® oligonucleotide array. The Affymetrix array (Affymetrix, Inc.Santa Clara, CA) is comprised of over 1,300,000 unique oligonucleotide features that represent greater than 38,500 well-substantiated human genes. The array was hybridized for 16 hours at 45°C with rotation at 60 rpm then washed and stained with a strepavidin, R-phycoerythrin conjugate stain on the Affymetrix Fluidicis Station 450. Signal amplification was done using biotinylated antistreptavidin. The arrays were scanned using the GeneChip® 3000 confocal laser scanner with autoloader. The images were analyzed and quality control metrics recorded using Affymetrix GCOS software version 1.4. Lastly, the expression value for each gene was calculated using dChip PM-only model based or Plier algorithm.

Data Analysis Methods

Pairwise comparisons were made as follows: Treated vs. Control (Y vs. D), Modified Drug vs Control (YM/ACY-H vs. D) and Treated vs. Modified Drug (Y vs. YM/ACH-Y) Cel files analyzed using the Bioconductor package of R Statistical programming. Limma analysis generated a reasonable number of changing genes between the samples.

The raw data were normalized by the GCRMA method (robust multi-array analysis). It is implemented in Bioconductor (http://www.bioconductor.org/). The raw signal intensity data were normalized, background corrected and summarized based on certain statistical models, and an expression value, in log2-scale, is obtained per chip per probe set. Then the null hypothesis was tested that there's no significant changes in gene expression between the treatment pairs. This was done by LIMMA and is also implemented in Bioconductor. It uses empirical Bayes method to estimate the variance in gene expression. One comparison was made, namely, High Grade vs. Low Grade. The raw p-values were adjusted by the Benjamnin-Hochberg method for false discovery rate (FDR) control. All data sets contained a significant number of genes with a p-value less than 0.05, which is that the probability that a gene is NOT differential expressed (false positive) is 1:20.

All expression data is filtered by p-value (0.05).

The raw p-values were adjusted by the Benjamnin-Hochberg method for false discovery rate (FDR) control to yield an adjusted p-value.

Western blot

Western blot is applied in this invention as a method to detect the specific proteins in treated and untreated cells with compounds in this invention, wherein the cells are breast, leukocyte, liver, ovarian, bladder, prostate, skin, bone, brain, leukemia, lung, colon, CNS, melanoma, renal and cervix cancer

Cells: targeted cells were grown in RPMI 1640 medium. 1.5 million cells were seeded in a T25 flask and grown for 24 hours before drug-treatment.

Drug-treatment: Cells cultures were replaced with fresh RPMI medium containing either 2.5 ul of DMSO (as control) [D]; or 10, 20, 30, 40, 80 ug/ml of tested compounds.

After 24 hours, aliquot of culture medium was taken out for Fibronectin determination (Western blot method).

Cell viability at 24 hours was determined by MTT assay. Cultures were replaced with RPMI medium (5 ml) with MTT and incubated for an hour. The formation of formazan was dissolved in 10 ml of DMSO and OD at 570nm was measured (MTT units).

Western Blot: Spent culture medium was mixed with SDS sample buffer, boiled for 3 minutes before loading to SDS gel. Samples were applied to a 6-10% SDS gel and electrophoresis was conducted with 100 volts for 2 hours. Protein was transferred to a nitrocellulose membrane electrophoretically. The nitrocellulose blot was incubated with the first antibody and second antibody (AP conjugated, Promega S3721). The immuno-bands were developed with BCIP/NBT color development system.

Determination of Western band intensity: The band-images of Western blot were captured with a digital camera and the intensity of bands was determined using "Image J" software.

This invention provides a composition comprising an effective amount of triterpenoidal saponins named as Xanifolia Y1, Y2, Y, Y7, Y8, Y9, Y10, Y0 or their derivatives for modulating the adhesion protein, reducing adhesion protein or

reducing the secretion of fibronectin, for treating chronic venous insufficiency, peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, expectorant, peripheral vascular disorders, cerebro-organic convulsion, cerebral circulation disorder, cerebral edema, psychoses, dysmenorrheal, hemorrhoids, episiotomies, peripheral edema formation or postoperative swelling; for reducing symptoms of pain; for reducing symptoms of stomach pain; for reducing symptoms of leg pain; for treating pruritis, lower leg volume, thrombosis, thromophlebitis; for treating rheumatism; for preventing gastric ulcers antispasmotic; blocking the migration, metastasis of cancer cells or inhibiting tumor growth. In an embodiment the method is administering contacting the compound in this application comprising Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10, Xanifolia (x), Escin or Aescin or a salt, ester, metabolite thereof. In an embodiment the compound may be selected from formulas (1A), (1B), (1C) and (1D). In an embodiment, the compound comprises a triterpene backbone, two angeloyl groups and sugar moiety. In an embodiment the compound(s) are selected from Compound A to X and A1 to X1 in the application. In an embodiment the compound(s) are selected from Compound Z1 to Z7 in the application.

This invention provides a method for reducing adhesion proteins or their receptors on cells, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment the method can block the migration, metastasis of cancer cells or inhibit the growth of cancers or anti-angiogenesis, wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer and cervix cancer.

This invention provides a method for interacting with adhesion proteins or their receptors, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, this invention provides a method of reducing the secretion of fibronectin. Furthermore the method is blocking the migration, metastasis of cancer

cells or treating a mammal cancers comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a composition comprises the molecular formula or compound in this invention. The cancers comprise Leukemia, Lung, Colon, CNS, Melanoma, Ovary, Renal, Prostate, Breast, bladder c, cervix, liver, bone , brain and Skin cancer.The compounds comprise Xanifolia Y0, Y1, Y2, Y, Y7,Y8, Y9, Y10, or a salt, ester, metabolite or derivative thereof. The compounds of this invention can be isolated from natural sources or synthesized.

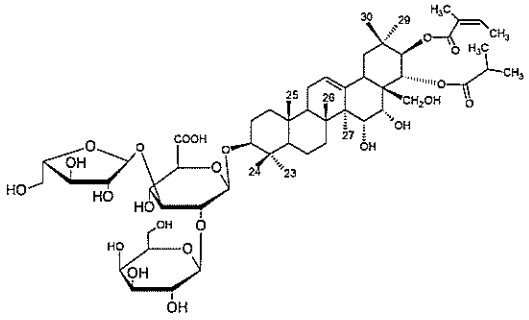
See experiments results in this application and see PCT/US05/31900, filed Spetember 7, 2006; U.S. Serial No. 10/906,303, filed February 14, 2005; International Application No. PCT/US04/43465, filed December 23, 2004; International Application No. PCT/US04/33359, filed October 8, 2004 and U.S. Serial No. 11/131551, filed May 17, 2005, PCT/US2007/077273, filed August 30, 2007, the contents of which are incorporated herein by reference.

A salt of compound comprise sodium salt, potassium salt or calcium salt.

A salt of compounds for inhibiting venous insufficiency, particularly hemorrhoids or inhibiting leg swelling, or peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, Expectorant, peripheral vascular disorders, cerebro-organic convulsion, cerebral circulation disorder, cerebral edema, psychoses, dysmenorrheal, hemorrhoids, episiotomies, hamonhoids, peripheral edema formation or postoperative swelling; for reducing symptoms of pain; for reducing symptoms of stomach pain; for reducing symptoms of leg pain; for treating pruritis, lower leg volume, thrombosis, thromophlebitis; for preventing gastric ulcers antispasmotic.

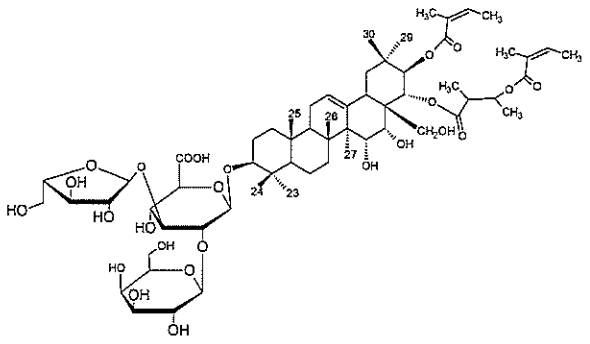
This invention provides a method of modulating the adhesion proteins or their receptors, reducing the adhesion ability of the cancer cells, wherein the modulating comprises the positive or negative regulating. In an embodiment, the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, the method is reducing the secretion of fibronectin. This invention provides a method of blocking the migration, metastasis of cancer cells or inhibiting cancer cell growth comprising administering an effective

amount of a pharmaceutical composition comprising a composition comprises the molecular formula or compound in this invention. The cancers comprise Leukemia cancer, Lung cancer, Colon cancer, CNS cancer, Melanoma cancer, ovarian cancer, renal cancer, Prostate cancer, Breast cancer, bladder cancer, cervix cancer, liver cancer, bone cancer, brain cancer and Skin cancer. The compounds of this invention can be isolated from natural sources or synthesized. In an embodiment the method is administering contacting the compounds, wherein the compound is selected from the following:



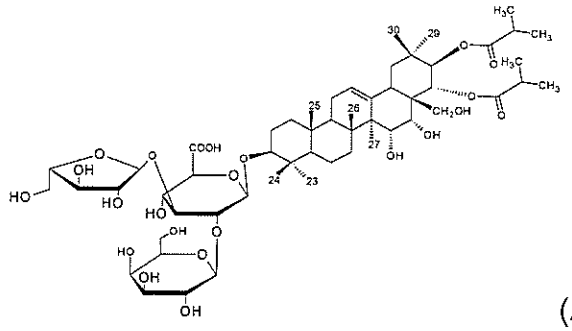
(Z1)

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-angeloyl, 22-O-(2-methylpropanoyl)-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,



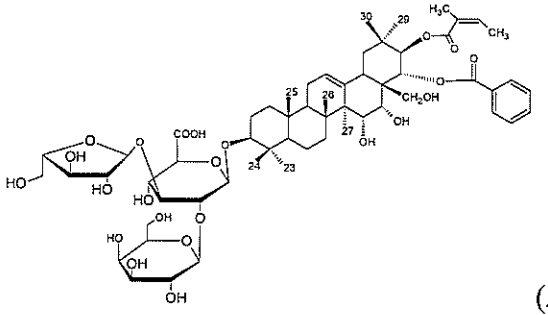
(Z2)

3-*O*-[*β*-D-galactopyranosyl-(1→2)]-*α*-L-arabinofuranosyl-(1→3)-*β*-D--glucuronopyranosyl-21-*O*-angeloyl-22-O-(angeloyl-2-methylbutanoyl) -3*β*, 15 *α*, 16*α*, 21*β*, 22*α*, 28-hexahydroxyolean-12-ene



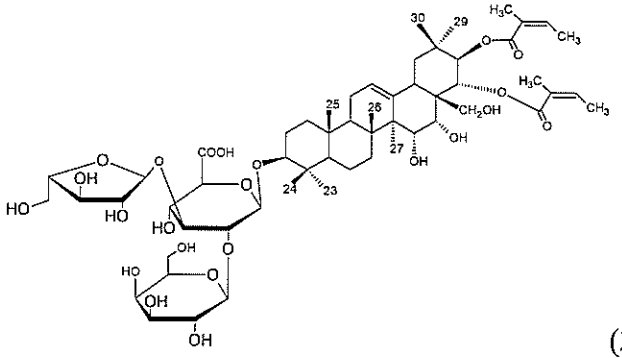
(Z3)

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-(2-methylpropanoyl), 22-O-(2-methylpropanoyl)-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,



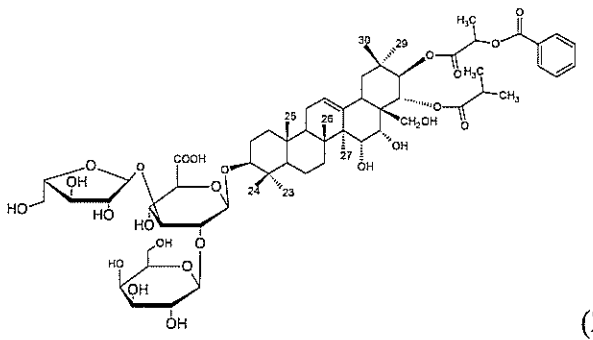
(Z4)

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-angeloyl, 22-O-benzoyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,



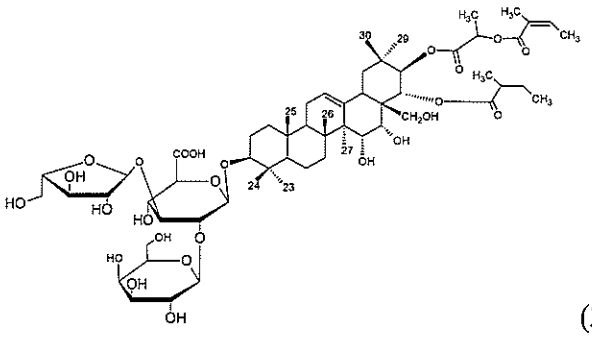
(Z5)

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-angeloyl, 22-O-angeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,



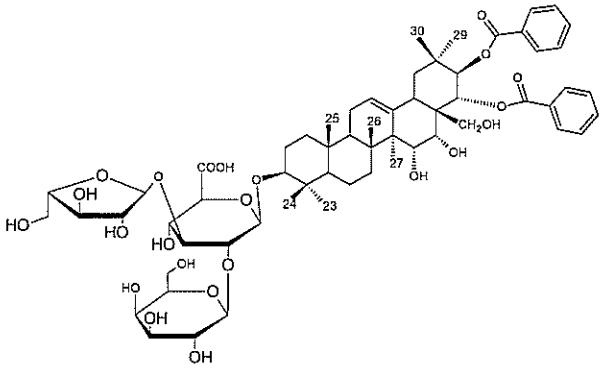
(Z6)

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-(2-methylpropanoyl)-O-benzoyl, 22-O-(2-methylpropanoyl)-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,



(Z7)

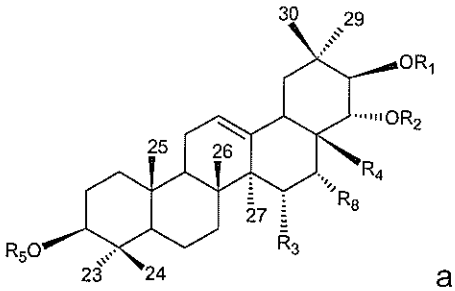
3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-(2-methylpropanoyl)-O-angeloyl, 22-O-(2- methylbutanoyl) -3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,



Z8

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-benzoyl, 22-O-benzoyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene

This invention provides uses of a compound selected from a compound with formula (1B), for modulating, regulating or interacting the adhesion protien, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, this invention provides a method of reducing the secretion of fibronectin :



also named as (1B),

or a salt, ester, metabolite or derivative thereof, wherein R1 comprises a group selected from hydrogen, angeloyl, acetyl, tigloyl, senecioyl, alkyl, dibenzoyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, acyl, aryl, heterocylic, heteroraryl and derivatives thereof; R2 comprises a group selected from hydrogen, angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and derivative thereof; R4 represents CH_2OR6 or COOR6, wherein R6 is selected from hydrogen, angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and derivative thereof; R3 is H or OH; wherein at least one of R1, R2,and R6 comprises a group selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and derivative thereof; R5 comprises a sugar moiety, wherein the sugar moiety comprises at least one sugar of, but is not limited to, D-glucose, D-galactose, L-rhamnose, L-arabinose, D-xylose, alduronic acid: D-glucuronic acid, D-galacturonic acid or a derivative thereof, or the combination thereof.

In an embodiment, R1 comprises a sugar moiety wherein substituted with two groups selecting from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic heteroraryl and a derivative thereof.

In an embodiment, R1 comprises a sugar moiety wherein substituted with at least one group selecting from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof.

In an embodiment, R2 comprises a sugar moiety wherein at least one group is selected from angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof.

In an embodiment, R2 comprises a sugar moiety or a side chain wherein at least two groups are selected from angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof.

In an embodiment, R4 comprises CH_2OR6 or COOR6 wherein R6 is a sugar moiety which comprises at least one group selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof.

In an embodiment, R4 comprises CH_2OR6 orCOOR6, wherein R6 is a sugar moiety which comprises at least two groups selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substitutedalkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof.

In an embodiment, R4 comprises CH_2OR6 or COOR6, wherein R6 is a sugar moiety which comprises at least two groups selected from angeloyl, acetyl, tigloyl and senecioyl.

In an embodiment, R4 comprises CH_2OR6 or COOR6 of formula (1B), at least two of R1, R2 and R6 comprise the group selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof.

In an embodiment, R4 comprises CH_2OR6 or COOR6 of formula (1B), at least two of R1, R2 and R6 comprise angeloyl, benzoyl, alkenoyl, or a derivative thereof.

In an embodiment, R4 is a side chain comprising CH_2OCOCH_3, CH_2COO-alkyl, CH_2OH, COOH, angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic or heteroraryl or a derivative thereof.

In a further embodiment, R5 comprises a sugar moiety, wherein the sugar moiety comprises one or more sugar of, but is not limited to glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, or alduronic acid: glucuronic acid, galacturonic acid, or derivatives thereof, or the combination thereof.

In an embodiment, R5 comprises a sugar moiety or a group capable of performing the function of the sugar moiety.

In an embodiment, the R5 represents H.

In an embodiment, R4 represents H, OH or CH_3.

In an embodiment, position C23, C24, C25, C26, C29 and C30 of the compound independently comprise CH_3, CH_2OH, CHO, COOH, COOa-lkyl, COO-aryl, COO-heterocyclic, COO-heteroaryl, CH_2Oaryl, CH_2O- heterocyclic, CH_2O- heteroaryl, alkyls group, acetyl group or derivatives thereof, particular CH3.

In an embodiment, R1 and R2 independently comprise an angeloyl group.

In an embodiment, R1 is a sugar moiety or a side chain which comprise two angeloyl groups.

In an embodiment, R1 and R2 independently comprise a benzoyl group.

In an embodiment, R1 is a sugar moiety which is substituted with two benzoly groups.

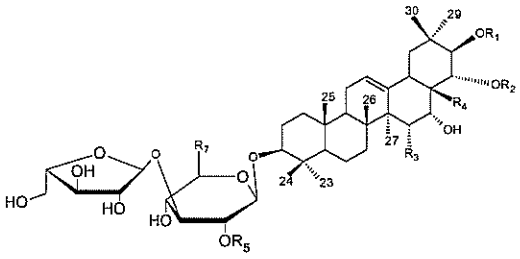
In an embodiment, R_3 represents H or OH.

In an embodiment, R8 may be OH

Substitution, deletion and/or addition of any group in the above-described compounds by other group(s) will be apparent to one of ordinary skill in the art based on the teachings of this application. In a further embodiment, the substitution, deletion and/or addition of the group(s) in the compound of the invention does not substantially affect the biological function of the compound. A composition comprising an effective amount of the compound selected from the above formula or

a salt, ester, metabolite or derivative thereof as a medicament for regulating or interacting with adhesion protien, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, this invention provides a method of reducing the secretion of fibronectin; wherein the medicament is for inhibiting tumor or cancer cell growth and for treating cancer, wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer.

This invention provides uses of a compound selected from a compound of formula (1D), for regulating or interacting with adhesion protien, wherein the adhesion proteins comprise of fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, this invention provides a method of reducing the secretion of fibronectin. :



and also named as (1D),

or a salt, ester, metabolite or derivative thereof, wherein R1 comprises a group selected from hydrogen, angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof; R2 comprises a group selected from hydrogen, angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof; R4 comprises CH_2OR6 or COOR6, wherein R6 comprises a group selected from hydrogen, angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof; R3 is H or OH; R5 comprises sugar moiety, D-glucose or D-galactose; R7 represents COOH; wherein at least one of R1 and R2 is an acyl.

In an embodiment, R7 is selected from CH_3, CH_2OH, COOH and COOalkyl.

In an embodiment, R7 is selected from CH_3, CH_2OH, CHO, COOH, COOalkyl, COOaryl, COO-heterocyclic, COO-heteroaryl, CH_2Oaryl, CH_2O- heterocyclic, CH_2O-heteroaryl, alkyls group, acetyl group and a derivative thereof.

In an embodiment, R1 represents a compound comprising a sugar moiety wherein the sugar moiety is substituted with at least two compounds selected from angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic , heteroraryl and a derivative thereof;

In an embodiment, R1 represents a compound comprising a sugar moiety substituted with at least one selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof;

In an embodiment, R2 represents a compound comprising a sugar moiety, wherein the sugar moiety substituted with at least one selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof;

In an embodiment, R2 represents a compound comprising a sugar moiety or a compound which substituted with at least two selected from, angeloyl, acetyl, tigloyl, senecioyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof;

In an embodiment, R4 comprises a group selected from CH_2OR6 and COOR6 wherein R6 is a sugar moiety which substituted with at least one selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof;

In an embodiment, R4 comprises a group selected from CH_2OR6 and COOR6 wherein R6 is a sugar moiety which substituted with at least two selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof;

In an embodiment, R4 comprises a group selected from CH_2OR6 and COOR6 wherein R6 is a sugar moiety which substituted with at least two selected from angeloyl, acetyl, tigloyl and senecioyl.

In an embodiment, R4 comprises a group selected from CH_2OR6 and COOR6 wherein R6 is a sugar moiety which substituted with at least two selected from

angeloyl, acetyl, tigloyl, senecioyl, benzoyl, alkanoyl, alkenoyl, dibenzoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and a derivative thereof; In an embodiment, R4 comprises a group seleced from CH_2OR6 and COOR6 wherein at least two of R1, R2 and R6 comprise a group selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic , heteroraryl and derivative thereof;
In an embodiment, R4 comprises a group selected from $CH_2OCOCH3$, $CH_2COOalkyl$, CH_2OH, COOH, angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl and derivative thereof.

In a further embodiment, R5 comprises a sugar moiety, glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid or galacturonic acid, or derivative thereof, or the combination thereof. In an embodiment, R5 comprises a compound capable of performing the function of the sugar moiety. In a further embodiment, the R5 comprises a H. In a further embodiment, R4 represents H or OH or CH_3.

In an embodiment, position 24 of the compound is CH_3 or CH_2OH, In a further embodiment, positions 23, 24, 25, 26, 29, 30 of the compound independently comprise CH_3, CH_2OH, CHO, COOH, COOalkyl, COOaryl, COO-heterocyclic, COO-heteroaryl, CH_2Oaryl, CH_2O- heterocyclic, CH_2O- heteroaryl, alkyls group, acetyl group or a derivative thereof.
In an embodiment, R5 comprises a sugar moiety comprising L-glucose, D-galactose, L-rhamnose, or/and L-arabinose.
In an embodiment, R1 and R2 independently comprise an angeloyl group; In a embodiment, R1 is a sugar moiety or rhamnose which comprise two angeloyl groups. In an embodiment, R3 represents H or OH; In a further embodiment, the compounds canbe isolated from natural sources or synthesized.

A sugar moiety is a segment of a molecule comprising one or more sugar groups. Substitution, deletion and/or addition of any group in the above-described compounds will be apparent to one of ordinary skill in the art based on the teaching

of this application. In a further embodiment, the substitution, deletion and/or addition of the group(s) in the compound of the invention does not substantially affect the biological function of the compound.

A method of inhibiting venous insufficiency, particularly hemorrhoids or inhibiting leg swelling, or peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, Expectorant, peripheral vascular disorders, cerebro-organic convulsion, cerebral circulation disorder, cerebral edema, psychoses, dysmenorrheal, hemorrhoids, episiotomies, hamonhoids, peripheral edema formation or postoperative swelling; for reducing symptoms of pain; for reducing symptoms of stomach pain; for reducing symptoms of leg pain; for treating pruritis, lower leg volume, thrombosis, thromophlebitis; for preventing gastric ulcers antispasmotic comprising administering to a subject, in need thereof, an effective amount of the composition of any one of the above compounds or a compound comprises a triterpene which comprises any two of angeloyl, tigloyl, senecioyl, perferable two angeloyl groups, and a sugar moiety, glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid or galacturonic acid, or a derivative thereof, or the combination thereof, preferable selected from glucuronic acid, galacturonic acid, glucose, galactose and arabinose. The method is regulating or interacting with adhesion protien, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK. In an embodiment, the method is reducing the secretion of fibronectin.

This invention provides a method for inhibiting the growth, migration, metastasis of cancer by altering the characteristic of membrane of cancer cell, wherein the characteristic comprise reducing adhesion protein; wherein the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK; wherein comprising inhibiting the secretion of fibronectin, wherein comprising administering to a subject, in need thereof, an appropriate amount of triterpenoidal saponins comprising two or more angeloyl groups, or a

compound comprises a triterpene which comprises any two of angeloyl, tigloyl, senecioyl, perferable two angeloyl groups, and a sugar moiety, glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid or galacturonic acid, or a derivative thereof, or the combination thereof, preferably selected from glucuronic acid, galacturonic acid, glucose, galactose and arabinose. This invention provides a composition comprising an effective amount of the compound of any one of compound selected from the above formula or a salt, ester, metabolite or derivative thereof as a medicament for reducing adhesion protein; wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK, for inhibiting the growth, migration, metastasis of cancer, wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer.

This invention also provides a composition comprising the above described compounds or their derivatives for reducing adhesion protein, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK; wherein comprising inhibiting the secretion of fibronectin, wherein for treating venous insufficiency, particularly hemorrhoids or inhibiting leg swelling, or peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, Expectorant, peripheral vascular disorders, cerebro-organic convulsion, cerebral circulation disorder, cerebral edema, psychoses, dysmenorrheal, episiotomies, hemonhoids, peripheral edema formation or postoperative swelling; for reducing symptoms of pain; for reducing symptoms of stomach pain; for reducing symptoms of leg pain; for treating pruritis, lower leg volume, thrombosis, thromophlebitis; for preventing gastric ulcers antispasmotic comprising administering to a subject, in need thereof, an effective amount of the composition.

In an embodiment of the above, the uses of compositions comprising any one of triterpenoid saponins with the following formula:

3-*O*-{[*β*-D-galactopyranosyl (1→2)]-[*α*-L-arabinofuranosyl (1→3)]-*β*-D-glucuronopyranoside butyl ester}-21-*O*-acetyl-22-*O*-angeloyl-3*β*,16*α*,21*β*,22*α*,28-pentahydroxyolean-12-ene.

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl -21-O-(3,4-diangeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene,

3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 24β, 28-heptahydroxyolean-12-ene,

3-*O*-[*β*-glucopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 24*β*, 28-hexahydroxyolean-12-ene,

3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*-(3,4-diangeloyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene,

3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene,

3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosy l-21-O-angeloyl, 22-O-(2-methylpropanoyl)-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

3-*O*-[*β*-D-galactopyranosyl-(1→2)]-*α*-L-arabinofuranosyl-(1→3)-*β*-D--glucuronopyranosyl-21-*O*-angeloyl-28-*O*-2-methylbutanoyl-3*β*, 15 *α*, 16*α*, 21*β*, 22*α*, 28-hexahydroxyolean-12-ene

This invention provides a composition comprising the compounds as described above effective in regulating or reducing adhesion protein, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK; inhibiting venous insufficiency, particularly hemorrhoids or inhibiting of leg swelling, and inhibiting cancer growth. The cancer includes but is not limited to bladder cancer, bone, cancer, skin cancer and ovarian cancer.

This invention also provides a composition for regulating or reducing adhesion protein, wherein the adhesion protein comprising fibronectin, integrins family, CD44, Myosin VI, vitronectin collagen, laminin, Glycosylation cell surface proteins, polyglycans and FAK; inhibiting venous insufficiency, particularly hemorrhoids or inhibition of leg swelling, or inhibiting cancer growth comprising any of compounds selected from the following compounds:

A) 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl (1→3)-β-D-glucuronopyranosyl-21, 22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

B) 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3, 4-diangeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene

C) 3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosyl (1→3)-(-D-glucuronopyranosyl-21, 22-O-diangeloyl-3*β*, 15*α*, 16*α*, 21*β*, 22*α*, 24*β*, 28-heptahydroxyolean-12-ene

D) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

E) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*-(3,4-diangeloyl)-*α*-rhamnopyranosyl-28-O-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

F) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

G) 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl (1→3)-β-D-glucuronopyranosyl -21, 22-O-dibenzoyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

H) 3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-(3,4- dibenzoyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene

I) 3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosyl (1→3)-(-D-glucuronopyranosyl -21, 22-O- dibenzoyl -3*β*, 15*α*, 16*α*, 21*β*, 22*α*, 24*β*, 28-heptahydroxyolean-12-ene

J) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*- dibenzoyl -3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

K) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*-(3,4-dibenzoyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

L) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*- dibenzoyl -3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

M) 3-O-[β-D-galactopyranosyl (1→2)]-β-D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl -21, 22-O-dibenzoyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

N) 3-O-[β-D-galactopyranosyl(1→2)]- β-D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3,4- dibenzoyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene

O) 3-O-[β-D-glucopyranosyl-(1→2)]-β-D-xyopyranosyl (1→3)-(-D-glucuronopyranosyl -21, 22-O- dibenzoyl -3*β*, 15*α*, 16*α*, 21*β*, 22*α*, 24*β*, 28-heptahydroxyolean-12-ene

P) 3-*O*-[*β*-D-galactopyranosyl (1→2)]-β-D-xyopyranosyl (1→3)-*β*-D-glucuronopyranosyl -21, 22-*O*- dibenzoyl -3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

Q) 3-*O*-[*β*-galactopyranosyl (1→2)]- β- xyopyranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*-(3,4- dibenzoyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

R) 3-*O*-[*β*-galactopyranosyl (1→2)]-β- xyopyranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*- dibenzoyl -3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

S) 3-O-[β-D-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl-21, 22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

T) 3-O-[β-D-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3,4-diangeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene

U) 3-O-[β-D-glucopyranosyl-(1→2)] - β- D-xyopyranosyl (1→3)-(-D-glucuronopyranosyl-21, 22-O-diangeloyl-3*β*, 15*α*, 16*α*, 21*β*, 22*α*, 24*β*, 28-heptahydroxyolean-12-ene

V) 3-*O*-[*β*-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-*β*-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

W) 3-*O*-[*β*-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*- (3, 4-diangeloyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

X) 3-*O*-[*β*-D-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-*β*-D-glucuronopyranosyl-21, 22-*O*-diangeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

This invention provides a composition for regulating or reducing adhesion protein, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK; wherein blocking the migration, metastasis of cancer cells inhibiting venous insufficiency, particularly hemorrhoids or inhibiting leg swelling, inhibiting cancer growth comprising any of the compounds selected from the following:

A1) 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-angeloyl,22-O-benzoyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

B1) 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-(3-angeloyl, 4-benzoyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene

C1) 3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosyl (1→3)-(-D-glucuronopyranosyl-21-O-angeloyl,22-O-benzoyl-3*β*, 15*α*, 16*α*, 21*β*, 22*α*, 24*β*, 28-heptahydroxyolean-12-ene

D1) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21-O-angeloyl, 22-benzoyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

E1) 3-*O*-[*β*-galactopyranosyl (1→2)]-*α*-arabinofuranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*-F) (3-angeloyl, 4-benzoyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

F1) 3-O-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21-O-angeloyl, 22-O-benzoyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene

G1) 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl (1→3)-β-D-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

H1) 3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-(3- benzoyl, 4-angeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene

I1) 3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosyl (1→3)-(-D-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl-3β, 15α, 16α, 21β, 22α, 24β, 28-heptahydroxyolean-12-ene

J1) 3-O-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene

K1) 3-O-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21-O-(3- benzoyl, 4-angeloyl)-α-rhamnopyranosyl-28-O-acetyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene

L1) 3-O-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene

M1) 3-O-[β-D-galactopyranosyl (1→2)]-β-D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl-21 -O-angeloyl, 22-O-benzoyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

N1) 3-O-[β-D-galactopyranosyl(1→2)]- β-D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3-angeloyl, 4- dibenzoyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene

O1) 3-O-[β-D-glucopyranosyl-(1→2)]-β-D-xyopyranosyl (1→3)-(-D-glucuronopyranosyl-21 -O-21 -O-angeloyl, 22-O-benzoyl -3β, 15α, 16α, 21β, 22α, 24β, 28-heptahydroxyolean-12-ene,

P1) 3-O-[β-D-galactopyranosyl (1→2)]- β- D-xyopyranosyl (1→3)-β- D-glucuronopyranosyl-2121 -O-angeloyl, 22-O-benzoyl -3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene

Q1) 3-*O*-[*β*-galactopyranosyl (1→2)]- β- xyopyranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*-(3-angeloyl, 4- dibenzoyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene,

R1) 3-*O*-[*β*-galactopyranosyl (1→2)]-β- xyopyranosyl (1→3)-*β*-glucuronopyranosyl--angeloyl, 22-O-benzoyl --3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene,

S1) 3-O-[β-D-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl--3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

T1) 3-O-[β-D-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3-benzoyl, 4-angeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene,

U1) 3-O-[β-D-glucopyranosyl-(1→2)] - β- D-xyopyranosyl (1→3)-(-D-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl--3*β*, 15*α*, 16*α*, 21*β*, 22*α*, 24*β*, 28-heptahydroxyolean-12-ene

V1) 3-*O*-[*β*-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-*β*-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

W1) 3-*O*-[*β*-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-*β*-glucuronopyranosyl-21-*O*- (3-benzoyl, 4-angeloyl)-*α*-rhamnopyranosyl-28-*O*-acetyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene

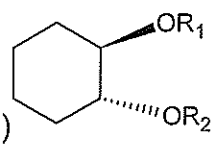
X1) 3-*O*-[*β*-D-galactopyranosyl (1→2)] - β- D-xyopyranosyl (1→3)-*β*-D-glucuronopyranosyl-21 -O-benzoyl, 22-O-angeloyl-3*β*, 16*α*, 21*β*, 22*α*, 28-pentahydroxyolean-12-ene.

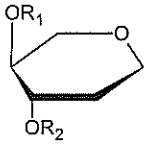
Triterpenoid saponins with the characteristic structures mentioned above in this invention can be used to inhibit venous insufficiency, particularly hemorrhoids or inhibit leg swelling, Triterpenoid saponins with the characteristic structures mentioned above in this invention can be used to block the migration, metastasis of cancer cells, reduce or inhibit cancer growth. The cancers are included but not limited to Leukemia cancer, Lung cancer, Colon cancer, CNS cancer, Melanoma cancer, Ovarian cancer, Renal cancer, Prostate cancer, Breast cancer, bladder cancer, cervix cancer, liver cancer, bone cancer, brain cancer and Skin cancer.

Triterpenoid saponins with the characteristic structures mentioned above in this invention can be used to affect cell membrane structure and adhesion process.. In an embodiment, it provides a method of regulating or reducing adhesion proteins to blocks the migration, metastasis of cancer cells, growth of cancers. In an embodiment, the method comprises reducing the adhesion ability of the cancer cells. In an embodiment, the adhesion proteins comprise IgSF CAM, Selectins, Integrin or Cadherins. In an embodiment, the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK;In an embodiment, the compound is a triterpenoidal saponin or sapogenin, wherein the triterpenoidal saponin comprises at least any one or two of an angeloyl group, tigloyl group, or senecioyl group, or their combinations thereof at carbon 21 and/or 22, or 28, directly attached to the sapogenin or attached to a sugar moiety can be used to to treat varicose vein disease, inhibit venous insufficiency, particularly hemorrhoids or inhibit leg swelling, reduce or inhibit cancer growth. In an embodiment, the compound is a five ring triterpene saponin comprising at least two angeloyl groups, tigloyl group, or senecioyl group, or their combinations thereof and a sugar moiety. The angeloyl groups are attached to a side chain at the end of the five rings and a sugar moiety is attached to a side chain of the ring at the other end of the five rings. In an embodiment, the compound comprises at least two angeloyl groups, a tigloyl group, or a senecioyl group, or combinations thereof and a sugar moiety. The angeloyl groups and the sugar moiety are attached to the side chains of the backbone of the compound respectively. In an embodiment, the angeloyl can be replaced by a functional group which functions as an angeloyl group. In an embodiment, a sugar moiety or chain is at C3 or other positions, comprising one or more sugar selected from, but is not limited to glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, or derivatives thereof, or the combination thereof preferably *D*-glucose, *D*-galactose, *L*-rhamnose, *L*-arabinose, alduronic acids of *D*- glucuronic acid or *D*-galacturonic acid, or their combinations thereof, or their derivatives thereof. In a further embodiment, CH_3 or CH_2OH or COOH or acetyl group may attach at C 23-30 independently. The activities of a saponin compound for regulating or inhibiting tumor cell growth are based on or attributed to its structure that has the

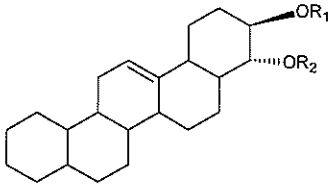
functional group(s) such as angeloyl group, tigloyl group, senecioyl group or acetyl group, or their combinations thereof.

This invention provides a composition comprising the compounds with the structure of:

(a) 

, or (b) 

wherein R1 and R2 comprise angeloyl groups, tigloyl groups, senecioyl groups or acetyl group or their combinations, preferable wherein the R1 and R2 comprise angeloyl groups. In an embodiment, R1 and R2 comprise compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.

(c) 

wherein R1 and R2 comprise angeloyl groups, tigloyl groups, senecioyl groups or acetyl group or their combinations, preferable wherein the R1 and R2 comprise angeloyl groups.

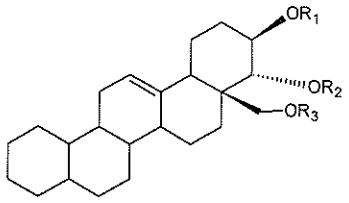
In an embodiment, R1 and R2 comprise compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.

In an embodiment, the compound further comprises a sugar moiety.

In a further embodiment, the sugar moiety comprises glucose, galactose or arabinose or combination thereof.

In an embodiment, the sugar moiety comprises at least one sugar, or glucose, or galactose, or rhamnose, or arabinose, or xylose, or alduronic acid, or glucuronic acid, or galacturonic acid, or their derivative thereof, or the combination thereof.

In an embodiment, the R1 or R 2 may be attached in other position of the structure.

(d) 

wherein R1, R2 or R3 comprise angeloyl groups, tigloyl groups, senecioyl groups or acetyl group or their combinations, preferable wherein at least two of the R1, R2 and R3 comprise angeloyl groups. In embodiment, at least two of R1, R2 and R3 comprise compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.

In an embodiment, at least one of R1, R2 and R3 comprise a sugar moiety comprising two compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.

In an embodiment, the compound comprises a sugar moiety. In an embodiment, the sugar moiety is attached at one end of structure (d), opposite to R1, R2 and R3. In a further embodiment, the sugar moiety comprises glucose, galactose or arabinose or combination thereof.

In a further embodiment, the sugar moiety comprises at least one sugar, or glucose, or galactose, or rhamnose, or arabinose, or xylose, or alduronic acid, or glucuronic acid, or galacturonic acid, or their derivative thereof, or the combination thereof.

In a further embodiment, the sugar moiety comprises one or more sugar selected from, but is not limited to glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, or derivatives thereof, or the combination thereof. In an embodiment, the R1, R 2 and R3 may be attached in other position of the structure.

In an embodiment, the compound is triterpenoid saponin comprise comprises at least two angeloyl groups, tigloyl groups, senecioyl groups or acetyl group or their combinations, preferable wherein at least two angeloyl groups.

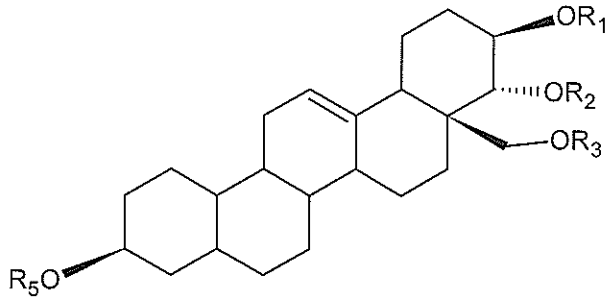
In an embodiment, at least two compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.

In an embodiment, at least one of the side bonds comprise a sugar moiety comprising two compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.

In an embodiment, the compound comprises a sugar moiety. In a further embodiment, the sugar moiety comprises glucose, galactose or arabinose or combination thereof.
In a further embodiment, the sugar moiety comprises at least one sugar, or glucose, or galactose, or rhamnose, or arabinose, or xylose, or alduronic acid, or glucuronic acid, or galacturonic acid, or their derivative thereof, or the combination thereof.

In a further embodiment, the sugar moiety comprises one or more sugar selected from, but is not limited to glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, or derivatives thereof, or the combination thereof.

In an embodiment, a triterpene comprise the following structure has activities of reducing adhesion proteins to blocks the migration, metastasis of cancer cells, growth of cancers.



wherein at least two of R1, R2 and R3 comprise compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof. In an embodiment, at least one of R1, R2 and R3 comprise a sugar moiety comprising two compounds selected from angeloyl, acetyl, tigloyl, senecioyl, alkyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof. In embodiment, R1, R2 or R3 comprise angeloyl groups, tigloyl groups, senecioyl groups or acetyl group or their combinations, preferable wherein at least two of the R1, R2 and R3 comprise angeloyl groups.

In an embodiment, R5 comprises sugar moiety. In an embodiment, the sugar moiety comprises at least one sugar, or glucose, or galactose, or rhamnose, or arabinose, or xylose, or alduronic acid, or glucuronic acid, or galacturonic acid, or their derivative thereof, or the combination thereof. In an embodiment, the sugar moiety comprises one or more sugar selected from, but is not limited to glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, or derivatives thereof, or the combination thereof. In an embodiment, the sugar moiety comprise glucose, galactose or arabinose, or combination thereof, or derivatives thereof. In an embodiment, the sugar moietiy comprise alduronic acids, galactose and arabinose, wherein the alduronic comprise glucuronic acid or galacturonic acid. In an embodiment, the sugar moiety comprise alduronic acids, glucose and arabinose, wherein the alduronic comprise glucuronic acid or galacturonic acid.

In an embodiment, the R1, R 2 and R3 may be attached in other position of the structure.

In an embodiment, the compound is triterpenoid saponin comprise comprises at least two angeloyl groups, tigloyl groups, senecioyl groups or acetyl group or their combinations, preferable wherein at least two angeloyl groups.

In an embodiment, at least two compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.

In an embodiment, at least one of the side bonds comprise a sugar moiety comprising two compounds selected from angeloyl, acetyl, tigloyl, senecioyl, benzoyl, dibenzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, or acid with 2 to 5 carbon or derivative thereof.
In an embodiment, the compound comprises a sugar moiety. In a further embodiment, the sugar moiety comprises glucose, galactose or arabinose or combination thereof.

In a further embodiment, the sugar moiety comprises at least one sugar, or glucose, or galactose, or rhamnose, or arabinose, or xylose, or alduronic acid, or glucuronic acid, or galacturonic acid, or their derivative thereof, or the combination thereof.

In a further embodiment, the sugar moiety comprises one or more sugar selected from, but is not limited to glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, or derivatives thereof, or the combination thereof.

A composition comprising an effective amount of compound selected from the above formula or a salt, ester, metabolite or derivative thereof as a medicament for regulating or reducing adhesion protein, blocking the migration, metastasis of cancer cells, inhibiting tumor or cancer cell growth and for treating cancer, wherein the cancers comprise breast, leukocyte, liver, ovarian, bladder, prostate, skin, bone, brain, leukemia, lung, colon, CNS, melanoma, renal and cervix cancer.

In a further embodiment, a compound or sapongenin comprises the structure (d) or (e) has anti-cancer or inhibiting virus activities.

A composition for regulating or reducing adhesion protein, blocking the migration, metastasis of cancer cells, treating cancers or inhibiting virus, comprising a compound, wherein the compound is a triterpene, which comprises at least two side chains which comprise angeloyl groups, wherein the side chains are at adjacent carbon in *trans* position. In an embodiment, the side chains are at alternate carbon in *cis* position. In an embodiment, the side chains are at alternate carbon in *trans* position. In an embodiment, the side chains are attached an acyl. In an embodiment, the side chains are attached an unsaturated group.

In an embodiment, the side chains are in non-adjacent carbon *cis* or *trans* position. In an embodiment, the side chains comprise a functional group capable of performing the function of angeloyl group.

The above compounds can be used for regulating or reducing adhesion protein, blocking the migration, metastasis of cancer cells, inhibiting tumor cell growth, reducing leg swelling, symptoms of chronic venous insufficiency, peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, expectorant, peripheral vascular disorders, by administering to a subject in need thereof, an effective amount of the above described compounds.

This invention provides a method for inhibiting tumor cell growth, regulating cell growth, reducing inflammation, in a subject, comprising administering to a subject, in need thereof, an effective amount of the compound which comprises any of the above structures to said subject. The cancers are included but not limited to Leukemia cancer, Lung cancer, Colon cancer, CNS cancer, Melanoma cancer, Ovarian cancer, Renal cancer, Prostate cancer, Breast cancer, bladder cancer, cervix cancer, liver cancer, bone cancer, brain cancer and Skin cancer.

This invention also provides a method for reducing swelling, reducing symptoms of chronic venous insufficiency, peripheral edema, antilipemic, chronic venous disease, varicose vein disease, varicose syndrome, venous stasis, Expectorant, peripheral

vascular disorders, cerebro-organic convulsion, cerebral circulation disorder, cerebral edema, psychoses, dysmenorrheal, hemorrhoids, episiotomies, peripheral edema formation or postoperative swelling; for reducing symptoms of leg pain; for treating pruritis, lower leg volume, for reducing symptoms of pain; thrombosis, thromophlebitis; for preventing gastric ulcers antispasmotic, comprising administering to a subject, in need thereof, an effective amount of the composition of this invention.

This invention provides a composition comprising the compounds provided in the invention for treating cancers; for inhibiting virus; for preventing cerebral aging; for improving memory; improving cerebral functions, for curing enuresis, frequent micturition, urinary incontinence,dementia, Alzheimer's disease, autism, brain trauma, Parkinson's disease or other diseases caused by cerebral dysfunctions; for treating arthritis, rheumatism, poor circulation, arteriosclerosis, Raynaud's syndrome, angina pectoris, cardiac disorder, coronary heart disease, headache, dizziness, kidney disorder; cerebrovascular diseasea; inhibiting NF-Kappa B activation; for treating brain edema, sever acute respiratory syndrome, respiratory viral diseases, chronic venous insufficiency, hypertension, chronic venous disease, anti-oedematous, anti inflammatory, hemonhoids, peripheral edema formation, varicose vein disease, flu, post traumatic edema and postoperative swelling;for inhibiting blood clot, for inhibiting ethanol absorption; for lowering blood sugar; for regulating the adrenocorticotropin and corticosterone level. This invention provides a composition for AntiMS, antianeurysm, antiasthmatic, antibradykinic, anticapillarihemorrhagic, anticephalagic, anticervicobrachialgic, antieclamptic, antiedemic, antiencaphalitic, antiepiglottitic, antiexudative, antiflu, antifracture, antigingivitic, antihematomic, antiherpetic, antihistaminic, antihydrathritic, antimeningitic, antioxidant, antiperiodontic, antiphlebitic, antipleuritic, antiraucedo, antirhinitic, antitonsilitic, antiulcer, antivaricose, antivertiginous, cancerostatic, corticosterogenic, diuretic, fungicide, hemolytic, hyaluronidase inhibitor, lymphagogue, natriuretic, pesticide, pituitary stimulant, thymolytic, vasoprotective, and venotonic treatment.

Alkenyl means unsaturated linear or branched structures and combinations thereof, having 1-7 carbon atoms, one or more double bonds therein. Non-limiting examples

of alkenyl groups include vinyl, propenyl, isopropenyl, butenyl, s- and t-butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, and hexadienyl.

An aryl is a functional group of organic molecule derived from an aromatic compound such as benzene, a 6-14 membered carbocyclic aromatic ring system cpmprising 1-3 benzene rings. If two or more aromatic rings are present, then the rings are fused together, so that adjacent rings share a common bond. Examples include phenyl and naphthyl. The aryl group may be substituted with one or more sunstitutes independnetly selected from halogen, alkyl or alkoxy.

Acyl is a functional group obtained from an organic acid by the removal of the carboxyl. Acyl groups can be written as having the general formula -COR, where there is a double bond between the carbon and oxygen. The names of acyl groups typically end in -yl, such as formyl, acetyl, propionyl, butyryl and benzoyl.
Benzoyl is one of acyls, C_6H_5COR, obtained from benzoic acid by the removal of the carboxyl.

Heterocyclic compound - a compound containing a heterocyclic ring which refers to a non-aromatic ring having 1-4 heteroatoms said ring being isolated or fused to a second ring selected from 3- to 7-membered alicyclic ring containing 0-4 heteroatoms , aryl and heteroaryl , wherein said heterocyclic comprises pyrrolidinyl , pipyrazinyl , morpholinyl , trahydrofuranyl , imidazolinyl , thiomorpholinyl, and the like.
Heterocyclyl groups derived from heteroarenes by removal of a hydrogen atom from any ring atom.
Alkanoyl is the general name for an organic functional group RCO-, where R represents hydrogen or an alkyl group. Preferably alkanoyl is selected from acetyl, propionoyl, butyryl, isobutyryl, pentanoyl and hexanoyl.
Alkenoyl is alkenylcarbonyl in which alkenyl is defined above. Examples are pentenoyl(tigloyl) and hexenoyl(angeloyl).
Alkyl is a radical containing only carbon and hydrogen atoms arranged in a chain, branched, cyclic or bicyclic structure or their combinations, having 1-18 carbon atoms. Examples include but are not limited to methyl, ethyl, propyl isopropyl, butyl,

s- and t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

Benzoyl alkyl substituted alkanoyl is refer to straight or branched C1-C6 alkanoyl substituted with at least one benzoyl and at least one alkyl, wherein the benzoyl is attached to a straight or branched C1-C6 alkyl. Preferably a benzoyl alkyl substituted alkanoyl is benzoyl methyl isobutanoyl.

A sugar moiety is a segment of molecule comprising one or more sugars or derivatives thereof or alduronic acid thereof.

Isobutyryl is Synonym of 2-Methylpropanoyl

Y and Y3 represent the same compound.

YM and (ACH-Y) represent the same compound.

This invention provides a method of altering the characteristic of cancer cell membrane to block the migration, metastasis of cancer cells or inhibit the growth of cancers or anti-angiogenesis.

This invention provides a method of inhibiting the growth, migration, metastasis of cancer by altering the characteristic of membrane of cancer cell, wherein the characteristic comprise adhesion protein; wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer, wherein the method is administering contacting Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10, or a salt, ester, metabolite thereof.

This invention provides a composition and method for inhibiting the growth, migration, metastasis of cancer by altering the adhesion characteristic of membrane of cancer cell, wherein the cancers comprise breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, renal cancer or cervix cancer, wherein the method is administering contacting Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10, or a salt, ester, metabolite thereof. In an embodiment the method is administering contacting the compound selected from formula in this application.

This application shows Xanifolia-Y is an alternate or supplemental agent to DNA-inhibition or microtubule-targeting drugs. It could be beneficial if it is used singly or in combination with other drugs of different mechanisms (block M-phase progression or DNA synthesis). Our inventions show combined effect of Xanifolia-Y and paclitaxel on inhibition of ES2 cells' growth (Detail in Experiment 14 U.S. Serial Nos.11/683198, filed on March 7, 2007)

Identify the binding target of Xanifolia-Y of adhesion proteins and signaling proteins in ovarian cancer cells.

In our animal studies, it was shown that Xanifolia-Y extended the life span of tumor bearing mice. (See Experiments 7, 8, 9 in U.S. Serial Nos.11/683198, filed on March 7, 2007,). The animals died sooner if the treatment of Xanifolia-Y was delayed (comparing results of treatments started from 1, 4 or 10 days after tumor inoculation). The results show that Xanifolia-Y inhibits migration or metastasis of the inoculated cancer cells. Ovarian carcinoma cells express high levels of adhesion molecules. Adhesion proteins are present in both cancer cells and mesothelial cells. While the lost of adhesion blocks of the protein accessibility due to a result of modulating by Xanifolia-Y, In an embodiment, the interaction of Xanifolia-Y with membrane alter the adhesion protein's binding site(s).

We have shown that Xanifolia-Y are cytotoxic to tumor cells, In an embodiment it kills ovarian cancer cells. Our inventions show that Xanifolia-Y inhibits cancer cell growth and prolongs life-span of tumor bearing mice. Our studies also indicate that the sooner the drug-treatment, the longer the life-span of the tumor bearing animals is extended. Xanifolia-Y also has an effect in blocking or inhibiting migration or metastasis. The delay of Xanifolia-Y-treatment allows more chances for cancer cells to metastasize to the mesothelium lining in the peritoneal cavity which resulted in more tumor growth and shorter life span. Adhesive molecules play an important role in cell migration and metastasis. It was shown in our studies that Xanifolia-Y inhibits cell attachment to culture flasks. Our experiment showed that Xanifolia-Y family inhibits the secrection of adhesion protein. Xanifolia-Y interferes with the function of the adhesive molecules. In embodiment Xanifolia-Y blocks the function of the adhesive molecules. In an embodiment, Xanifolia-Y modulates adhesive proteins. It is masking the adhesive proteins. In an embodiment, Xanifolia-Y indirectly alters membrane structure that cause changes in protein conformation, or locations and

result in loss of adhesion process. In an embodment, the adhesion proteins comprise fibronectin, integrins family, Myosin, vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK, particular fibronectin.

Fibronectin is a kind of glycoprotein that binds to membrane spanning receptor proteins comprising the integrins, collagen, fibrin and heparin sulfate. Fibronectin has been implicated in tumor development and metastasis. This application provides methods and compositions for modulating the gene expression of fibronectin, inhibiting the secretion of fibronectin, reducing the receptors of fibronectin, reducing the adhesion ability fibronectin, inhibiting the metastasis, or inhibiting cancer growth, wherein the method and composition comprises administering to the said subject as effective amount of compounds selected in this appliaction.

Vitronectin is an abundant glycoprotein found in blood plasma and the extracellular matix. Vitronectin is involved in hemostasis and tumot malignancy. This application provides methods and compositions for modulating the gene expression of vitonectin, reducing the receptors of vitronectin, reducing the adhesion ability Vitronectin, inhibiting the metastasis, and inhibiting cancer growth, wherein the method and composition comprises administering of compounds selected in this appliaction.

Integrins are cell surface receptors that interact with the extracellular matix. They define cellular shape, mobility, and regulate the cell cycle. Integrin plays a role in the attachment of cells to other cells, and also plays a role in the attachment of a cell to the material part of a tissue. Besides the attachment role, integrin also plays a role in signal transduction. This application provides method and composition for modulating the gene expression of integrins, wherein comprising inhibiting integrins, inhibititng the adhesion ability of integrins, inhibiting cancer cell metastasis and inhibiting cancer growth, wherein the method and composition comprise administering of compounds selected in this appliaction.

Laminins are a family of glycoproteins that are an integral part of the structural scaffolding of basement membranes in almost every animal tissue. They are secreted and incorporated into cell-associated extrcellular matrices. Inhibiting the

gene expression of laminins will reduce the adhesion ability of cells in order to inhibit the cell migration and metastasis of cancer cells. This application provides method and composition for modulating the gene expression of laminins, wherein comprising inhibiting laminins, inhibititng the adhesion ability of laminins inhibiting cancer cell metastasis and inhibiting cancer growth, wherein the method and composition comprise administering of compounds selected in this appliaction.

CAM (cell adhesion molecules) are proteins located on the cell surface which inolve with binding with other cells in an adhesion process. Inhibiting the gene expression of CAM will reduce the adhesion ability of cells and further inhibit the cell migration and metastasis of cancer cells. This application provides method and composition for modulating the gene expression of CAM, wherein comprising inhibiting CAM, inhibititng the adhesion ability of CAM, inhibiting cancer cell metastasis and inhibiting cancer growth, wherein the method and composition comprise administering of compounds selected in this appliaction.

Collagen is the main protein of conective tissue in mammal. Inhibiting the gene expression of collagen will reduce the adhesion ability of cells in order to inhibit the cell migration and metastasis of cancer cells. This application provides methods and compositions for modulating the gene expression of laminins, wherein comprising inhibiting laminins, inhibititng the adhesion ability of laminins inhibiting cancer cell metastasis and inhibiting cancer growth, wherein the method and composition comprise administering of compounds selected in this appliaction.

Tenascin-C (Tn-C) is an extracellular matrix protein on the cell. It is a positive factor for cancer growth, invasion and angiogenesis activities. This application provides methods and compositions for inhibiting Tenascin-C and inhibiting cancer growth, wherein the methods and compositions comprise administering of compounds selected in this appliaction.

Angiogenesis is a process involving the growth of new blood vessels. It is a normal process in growth and development. However, this is also a fundamental step in the transition of tumors from a dormant state to a malignant state. The angiopoietins are

protein growth factors that modulate angiogenesis. The identified angiopoietins comprise angiopoietin 1, angiopoietin 2, angiopoietin 3, angiopoietin 4, angiopoietin 5, angiopoietin 6, angiopoietin 7, angiopoietin-like 1, angiopoietin-like 2, angiopoietin-like 3, angiopoietin-like 4, angiopoietin-like 5, angiopoietin-like 6, and angiopoietin-like 7. In an embodiment, the angiopoietin 1 is a positive foctor to promote the new blood vessels. In embodiment, the angiopoietin 2 is antagonist of angiopoietin 1, which is a negative factor for the growth of new blood vessels. This application provides methods and compositions for modulating angiopoietin and inhibiting cancer growth; wherein the cancers comprise breast, leukocyte, liver, ovarian, bladder, prostate, skin, bone, brain, leukemia, lung, colon, CNS, melanoma, renal and cervix cancer, wherein the methods and compositions comprise administering to the said subject as effective amount of compounds selected in this appliaction. The compounds in this application are positive regulating angiopoietin 2. The compounds in this application are negative regulating the angiopoietin 1. The results of the micro array experiment showed that compound Y and YM (ACH-Y) modulate the gene expression of angiopoietin family in ES2 cells. They promote angiopoietin 2 and inhibit angiopoietin 1 and angiopoietin-like 1 and angiopoietin-like 4.

The compounds in this application are anti-angiogenesis, inhibiting cancer cell metastasis and inhibiting cancer growth, wherein the compounds comprise Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10, ACH-Y or a salt, ester, metabolite thereof and compounds selected from formula (1A), (1B), (1C) and (1D). In an embodiment the method is administering contacting the compound in this application comprising Xanifolia Y0, Y1, Y2, Y, Y7, Y8, Y9, Y10, Xanifolia (x), Escin or Aescin or a salt, ester, metabolite thereof. In an embodiment the compound may be selected from formulas (1A), (1B), (1C) and (1D). In an embodiment, the compound comprises a triterpene backbone, two angeloyl groups and sugar moiety. In an embodiment the compound(s) are selected from Compound A to X and A1 to X1 in the application. In an embodiment the compound(s) are selected from Compound Z1 to Z7 in the application.

Data obtained from our Microarray experiments disclose that Xanifolia Y modulates gene expression of the following genes (represented by gene symbol):

Gene Symbol: ABL2, ADAMTS1, AKR1C3, AMIGO2, ANGPT2, ANKRD11, AP2B1, APEH, APLP2, ARL10C, ARMC4, ARMCX1, ARMCX6, ARNTL2, ARNTL2, ATF3, ATP6V0E, ATP6V1B2, ATP6V1C1, ATP6V1C1, BCL2A1, BCL6, BRI3, BTD, C14orf109, C14orf78, C17orf32, C6orf65,C9orf10, C9orf103, CAD, CAV1, CAV2, CBLL1, CCL20, CD33L3, CEBPB, CEP4, CFH /// CFHL1, CHRDL1, CITED2, CITED2, CLDN14, CLN8, CLTA, CNAP1, COG6, COL18A1, COL4A2, COL5A1, COL5A2, COL6A3, COPG, CPM, CPNE3, CPSF1, CSRP2BP, CSTB, CTNS, CXCL2, DDB1, DDIT3, DDX20, DKFZP564I1171, DKFZP586J0619, DUSP10, DUSP10, DYRK3, EEF2K, EFEMP1, EMP1, EVC, EVI2A, EXT2, FAM62A, FER1L3, FLJ14466, FLNA, FN1, FN1, GANAB, GDF15, GEM, GNPDA1, GPAA1, GPC6, GPNMB, GPNMB, GUSB, H2AFV, H2AFV, HDAC9, HDLBP, HECW2, HMGA2, HMOX1, HSDL2, HSPBAP1, HSPC196, HYOU1, IDS, IGFBP3, IKBKAP, INSIG1, IPO4, IRS2, JAG1, KDELR3, KIAA0251, KIAA0586, KIAA1211, KIAA1462, KIAA1706, KIAA1754, KRT18, KRT7, KRTAP4-7, LAMP2, LEPR, LEPREL1, LHFPL2, LIF, LOC286044, LOC339229, LOC90693, LRRC8E, MAFG, MAGED2, MCTP1, MGC16291, MGC19764, MGC5618, MRPS30, MRPS31, MTERFD3, MYH9, NAGA, NAV2, NCSTN, NEK9, NEU1, NFKBIZ, NMT2, NPC2, NSUN5C, NTNG1, NUP188, OACT2, OS9, P4HA1, P8, PALM2-AKAP2, PALM2-AKAP2, PARVA, PBX2, PDE4DIP, PDIA4, PDIA6, PEG10, PHF19, PIK4CA, PLEKHM1, PLOD1, PLOD2, PPP1R15A, PPP1R15A, PRKDC, PRSS23, PRSS23, PSEN2, PSMD1, PTPRF, PTPRJ, RAB32, RAB9A, RG9MTD1, RGS4, RHOQ, RND3, RNF25, RNPEP /// UBE2V1 /// Kua /// Kua-UEV, RNU17D, ROBO4, RRAGC, RRS1, SEC31L1, SERPINB2, SERPINB7, SESN2, SGEF, SGSH, SKIV2L, SLC25A21, SLC35A3, SLC3A2, SMARCA1, SNAPC1, SNF1LK, SPOCD1, SPTAN1, SQSTM1, ST3GAL6, STC2, STX3A, TFPI2, TFPI2, TGFBI, TGM2, THRAP1, TLN1, TMEM60, TNFAIP3, TRIB3, TRIO, TSC2, UAP1L1, UBAP2L, UPP1, URB, USP11, USP5, VDR, WDR4, YTHDF2, ZCCHC9, ZDHHC20, ZFHX1B, ZNF185, ZNF278, ZNF690, ZNF697

Our experiment disclosed that Xanifolia Y and ACH-Y inhibited genes expression of the following genes: FN1, ITGAV, LAMA4, LAMB2, LAMC1, LAMB1, LAMB1, LAMA4, LAMA5, LAMC1, LAMA2, LAMB1, LAMA3, SCAMP1, TICAM2, SCAMP1, TICAM2, SCAMP1, SCAMP1, CAMK2B, DL1, ICAM3,CEECAM1,ICAM5,SCAMP1, CAMK1G, CAMSAP1, MCAM, CAMTA1, CKN1, ALCAM, DCAMKL2, CEACAM3,

CAMK2D, CAMK2B, SCAMP5, CAMK4, NCAM1, CAMK2G, MYH9, MYH10, MYO1D, MYO5A, MYLK, MYO6, MYO5A, MYO1C, MYLK, MYO6, MYLC2PL, MYO10, MYO6, TPM3, MYO1C, BECN1, MYO1E, TPM3, M-RIP, MYO1B, MYO10, MYO5A, M-RIP, MYO10, MYL6, MYOHD1, BECN1, TPM4, MYLK, MYH10, MYOHD1, LOC221875, LOC402643, MYO15B, LOC129285, MYH11, MYO1B, MYO1C, MYO9B, CDH13, CTNNAL1, CDH13, CDH12, CTNNB1, CDH5, CTNND1, CDH2, CTNNA1, CDH2, PCDHB16, CTNNA1, CELSR2, PCDHB6, PCDHB7, CTNND2, PCDHGC3, PCDHGB4, PCDHGA8, PCDHGA12, PCDHGC5 , PCDHGC4 , PCDHGB7, PCDHGB6, PCDHGB5, PCDHGB3, PCDHGB2, PCDHGB1, PCDHGA11, PCDHGA10 , PCDHGA9, PCDHGA7, PCDHGA6, PCDHGA5, PCDHGA4 , PCDHGA3 , PCDHGA2, PCDHGA1, CTNND1, CDH23, PCDHB12, PCDHB10, PCDH18, CDH20, PCDH9, PCDHGA12 , PCDHGA11, PCDHGA10, PCDHGA6, PCDHGA5, PCDHGA3, PCDH7, CDH18, CDH6, CCBE1, COL10A1, COL12A1, COL13A1, COL18A1, COL1A1, COL21A1, COL4A1, COL4A2, COL4A5, COL4A6, COL5A1, COL5A2, COL6A1, COL6A2, COL6A3, COL9A1, MMP9, P4HA1, P4HA2, P4HB, PCOLCE, PCOLCE2, PCOTH, PLOD1, PLOD2, PLOD3, CIB1, ILK, ITGA2, ITGA3, ITGA4, ITGA6, ITGAV, ITGB1, ITGB1BP1, ITGB2, ITGB5, ITGBL1, TNC, EMILIN1, ICAM1, HSPG2, HPSE, HS2ST1,SDC2,

This invention provides methods of regulating adhesion proteins which are important for blocking migration, metastasis of cancer cells, and inhibiting the growth of cancers. In an embodiment, the method comprises reducing the adhesion ability of the cancer cells.. In an embodiment, the adhesion protein comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, Glycosylation cell surface proteins, polyglycans, cadherin, heparin, tenascin, CD 54, CAM, elastin and FAK, particular for fibronectin.

The following results are obtained from MicroArray experiments:
Y/D is the ratio (in folds) of gene expression in cells treated with compound Y as compared with those of the no drug control (D),
YM/D is the ratio of gene expression in cells treated with compound YM (ACH-Y, Y without sugar moiety) compared with those of the no drug control (D)

Table 1: Effect of Y and YM on fibronectin expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
212464_s_at	-2.7	-1.1	FN1	fibronectin 1
216442_x_at	-2.6	-1.1	FN1	fibronectin 1
211719_x_at	-2.6	-1.2	FN1	fibronectin 1
210495_x_at	-2.5	-1.1	FN1	fibronectin 1

The results of the microarray experiment showed that compound Y and YM(ACH-Y) inhibit fibronectin expression; The expression ratio of compound Y/Y3 to the control are -2.7, -2.6, -2.6, -2.5 folds detected by gene probes 212464_s_at; 216442_x_at; 211719x_at and 210495_x_at, respectively. These results indicate Y/Y3 inhibits fibronectin expression; wherein the YM/ACH-Y also show minor fibronectin inhibition with the inhibiting ratio of -1.1, -1.1, -1.2, -1.1 folds by gene probes 212464_s_at; 216442_x_at; 211719_x_at and 210495_x_at, respectively . The results indicate that while YM is active but is less potent than Y/Y3.

Table 2. Effects of Y and YM on integrin (vitronectin receptor) expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
202351_at	-1.8	-1.3	ITGAV	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)
236251_at	-1.4	-1.4	ITGAV	Integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)

The results of the micro array experiment showed that compound Y and YM(ACH-Y) inhibit integrin (vitronectin receptor) expression; wherein the inhibiting ratio of compound Y/Y3 to the control are -1.8, -1.4, folds as detected by different probes; wherein the inhibiting ratio of YM (ACH-Y) to the control are -1.3, -1.4 folds.

Table 3: Effects of Y and YM on laminin expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
202202_s_at	-2.2	-2.0	LAMA4	laminin, alpha 4
216264_s_at	-2.0	-2.0	LAMB2	laminin, alpha 5
200770_s_at	-1.9	-1.1	LAMC1	laminin, alpha 6
211651_s_at	-1.6	-1.7	LAMB1	laminin, alpha 7

201505_at	-1.6	-2.0	LAMB1	laminin, beta 1

The results of the micro array experiment showed that compound Y and YM(ACH-Y) inhibit laminin expression; The expression ratio of compound Y/Y3 to the control are -2.2, -2.0, -1.9, -1.6, -1.6 folds as detected by different probes; wherein the inhibiting ratio of YM/ACH-Y to the control are -2.0, -2.0, 1.1, -1.7, -2.0 folds.

Table 4: Effects of Y and YM on CAM expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
201952_at	-1.9	-1.4	ALCAM	activated leukocyte cell adhesion molecule
201951_at	-1.9	-1.7	ALCAM	activated leukocyte cell adhesion molecule
212425_at	-1.7	-1.5	SCAMP1	Secretory carrier membrane protein 1
240655_at	-1.6	-1.3	ALCAM	Activated leukocyte cell adhesion molecule
212417_at	-1.4	-1.4	SCAMP1	secretory carrier membrane protein 1
239431_at	-1.3	-1.3	TICAM2	toll-like receptor adaptor molecule 2
212416_at	-1.3	-1.1	SCAMP1	secretory carrier membrane protein 1
228234_at	-1.3	-1.3	TICAM2	toll-like receptor adaptor molecule 2
206667_s_at	-1.3	-1.5	SCAMP1	secretory carrier membrane protein 1

The micro array experiment showed that compound Y and YM(ACH-Y) inhibit gene expression related to the adhesion molecule; wherein the inhibiting ratio of compound Y/Y3 to the control are -1.3 to -1.9 folds as detected by different probes; wherein the inhibiting ration of YM/ACH-Y to the control are -1.1 to -1.7 folds.

Table 5: Effects of Y and YM on collagen expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
217428_s_at	-3.0	-1.2	COL10A1	collagen, type X, alpha 1(Schmid metaphyseal chondrodysplasia)
231766_s_at	-2.8	-2.4	COL12A1	collagen, type XII, alpha 1
201438_at	-2.4	-1.5	COL6A3	collagen, type VI, alpha 3
1556138_a_at	-2.2	-2.8	COL5A1	Collagen, type V, alpha 1
211809_x_at	-2.0	-1.5	COL13A1	collagen, type XIII, alpha 1
207543_s_at	-2.0	-1.5	P4HA1	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide I

213992_at	-2.0	-1.9	COL4A6	collagen, type IV, alpha 6
211343_s_at	-1.9	-1.7	COL13A1	collagen, type XIII, alpha 1
211966_at	-1.8	-1.7	COL4A2	collagen, type IV, alpha 2
200656_s_at	-1.8	-1.2	P4HB	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide (protein disulfide isomerase-associated 1)
209081_s_at	-1.7	-1.5	COL18A1	collagen, type XVIII, alpha 1
202619_s_at	-1.7	-1.2	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2
203325_s_at	-1.7	-2.8	COL5A1	collagen, type V, alpha 1
200827_at	-1.7	-1.2	PLOD1	procollagen-lysine 1, 2-oxoglutarate 5-dioxygenase 1
221730_at	-1.6	-1.6	COL5A2	collagen, type V, alpha 2
202311_s_at	-1.6	-3.6	COL1A1	collagen, type I, alpha 1
213110_s_at	-1.6	-2.2	COL4A5	collagen, type IV, alpha 5 (Alport syndrome)
212091_s_at	-1.6	-1.9	COL6A1	collagen, type VI, alpha 1
213290_at	-1.6	-1.5	COL6A2	collagen, type VI, alpha 2
211981_at	-1.6	-2.2	COL4A1	collagen, type IV, alpha 1
200654_at	-1.6	-1.3	P4HB	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide (protein disulfide isomerase-associated 1)
212489_at	-1.5	-4.1	COL5A1	collagen, type V, alpha 1
202620_s_at	-1.4	-1.3	PLOD2	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2
202733_at	-1.4	-1.9	P4HA2	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II
208535_x_at	-1.4	-1.2	COL13A1	collagen, type XIII, alpha 1
202185_at	-1.3	-1.1	PLOD3	procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3
202465_at	-1.3	-1.6	PCOLCE	procollagen C-endopeptidase enhancer

221729_at	-1.3	-1.8	COL5A2	collagen, type V, alpha 2
242324_x_at	-1.3	-1.8	CCBE1	collagen and calcium binding EGF domains 1
1568611_at	-1.3	-2.4	P4HA2	Procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II

The results of the micro array experiment showed that compound Y and YM(ACH-Y) inhibit collagen expression. The expression ratio of compound Y/Y3 to the control range from -1.3 to -3.0 folds; wherein the expression ratio of YM/ACH-Y to the control range from -1.1 to -3.6 folds

Table 6: Effects of Y and YM on integrin expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
205422_s_at	-1.9	-2.0	ITGBL1	integrin, beta-like 1 (with EGF-like repeat domains)
202351_at	-1.8	-1.3	ITGAV	integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)
1557080_s_at	-1.7	-2.5	ITGBL1	Integrin, beta-like 1 (with EGF-like repeat domains)
214927_at	-1.7	-1.8	ITGBL1	Integrin, beta-like 1 (with EGF-like repeat domains)
205885_s_at	-1.7	-2.0	ITGA4	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)
213416_at	-1.6	-1.7	ITGA4	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)
215177_s_at	-1.6	1.1	ITGA6	integrin, alpha 6
205884_at	-1.6	-1.7	ITGA4	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)
1555349_a_at	-1.6	-1.4	ITGB2	integrin, beta 2 (antigen CD18 (p95), lymphocyte function-associated antigen 1; macrophage antigen 1 (mac-1) beta subunit)
227259_at	-1.6	-1.1	CD47	CD47 antigen (Rh-related antigen,

				integrin-associated signal transducer)
201474_s_at	-1.6	-1.5	ITGA3	integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)
214021_x_at	-1.5	-2.2	ITGB5	Integrin, beta 5
201656_at	-1.5	-1.1	ITGA6	integrin, alpha 6

The results of the micro array experiment showed that compound Y and YM(ACH-Y) inhibit gene expression related to the integrin family in ES2 cells. The expression ratio of compound Y/Y3 to the control are ranging from -1.5 to -1.9 folds; wherein the expression ratio of YM/ACH-Y to the control are ranging from -1.1 to -2.5 folds.

Table 7: Effects of Y and YM on myosin expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
211926_s_at	-2.2	-1.2	MYH9	myosin, heavy polypeptide 9, non-muscle
212372_at	-1.7	-1.4	MYH10	myosin, heavy polypeptide 10, non-muscle
212338_at	-1.7	-2.1	MYO1D	myosin ID
204527_at	-1.6	-1.2	MYO5A	myosin VA (heavy polypeptide 12, myoxin)
202555_s_at	-1.6	-1.2	MYLK	myosin, light polypeptide kinase /// myosin, light polypeptide kinase
203215_s_at	-1.6	-1.6	MYO6	myosin VI
225080_at	-1.5	-1.4	MYO1C	Myosin IC
224823_at	-1.5	-1.4	MYLK	myosin, light polypeptide kinase

The results of the micro array experiment showed that compound Y and YM(ACH-Y) inhibit gene expression related to the myosin family in ES2 cells. The expression ratio of compound Y/Y3 to the control are ranging from -1.5 to -2.2 folds; wherein the expression ratio of YM/ACH-Y to the control are ranging from -1.2 to -2.1 folds.

Table 8: Effects of Y and YM on cadherins expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
244091_at	-2.0	-1.7	CDH13	Cadherin 13, H-cadherin (heart)
202468_s_at	-1.9	-1.6	CTNNAL1	catenin (cadherin-associated protein), alpha-like 1
204726_at	-1.8	-1.7	CDH13	cadherin 13, H-cadherin (heart)

207149_at	-1.7	-2.2	CDH12	cadherin 12, type 2 (N-cadherin 2)
201533_at	-1.5	1.2	CTNNB1	catenin (cadherin-associated protein), beta 1, 88kDa
204677_at	-1.5	-1.1	CDH5	cadherin 5, type 2, VE-cadherin (vascular epithelium)
208407_s_at	-1.5	-1.7	CTNND1	catenin (cadherin-associated protein), delta 1
203440_at	-1.4	1.0	CDH2	cadherin 2, type 1, N-cadherin (neuronal)
210844_x_at	-1.4	-1.2	CTNNA1	catenin (cadherin-associated protein), alpha 1, 102kDa

The results of the micro array experiment showed that compound Y and YM(ACH-Y) inhibit gene expression of cadherins family in ES2 cells.

Table 9: Effects of Y and YM on tenascin-C expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
201645_at	-3.2	1.0	TNC	Tenascin C (hexabrachion)

The results of the micro array experiment showed that compound Y inhibit gene expression of cadherins family in ES2 cells.

Table10: Effects of Y and YM on heparin sulfate expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
201655_s_at	-2.4	-1.3	HSPG2	heparan sulfate proteoglycan 2 (perlecan)
219403_s_at	-1.4	-1.3	HPSE	Heparanase
203284_s_at	-1.3	-1.7	HS2ST1	heparan sulfate 2-O-sulfotransferase 1

The results of the micro array experiment showed that compound Y inhibit gene expression of heparin sulfate family in ES2 cells.

Table 11: Effects of Y and YM on CD54 expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
202638_s_at	1.6	2.3	ICAM1	intercellular adhesion molecule 1 (CD54), human rhinovirus receptor

The results of the micro array experiment showed that compound Y stimulate gene expression of CD54 in ES2 cells.

Table 12: Effects of Y and YM on angiopoietin expression in ES2 cells

Probe Set ID	Y/D	YM/D	Gene.Symbol	Gene.Title
205572_at	3.5	1.4	ANGPT2	angiopoietin 2
211148_s_at	2.5	1.4	ANGPT2	angiopoietin 2
205609_at	-1.1	-1.2	ANGPT1	angiopoietin 1
221009_s_at	-1.2	-1.4	ANGPTL4	angiopoietin-like 4
227533_at	-1.5	-2.3	ANGPTL1	Angiopoietin-like 1

The results of the micro array experiment showed that compound Y and YM(ACH-Y) modulate the gene expression of angiopoietin family in ES2 cells. There is a up regulation of (positive regulating on) angiopoietin 2 and a down regulation of (negative regulating on) angiopoietin 1 and angiopoietin-like 1 and angiopoietin-like 4.

Fibronectin secretion studies summary:

Reduction of Fibronectin secretion from ES2 cells after xanifolia-Y treatment.

(Results of F1 and F3) In these experiments, we established and described the basic phenomenon that Y-treatment of ES2 cancer cells cause inhibition of fibronectin secretion. With a Western blot assay, we showed that ES2 cells without drug treatment (DMSO control) secret Fibronectin to medium and the amount of Fibronectin accumulated with time. However, no or only minimally secretion of Fibronectin was observed in cell culture treated with Xanifolia-Y. Inhibition of Fibronectin was observed as early as 8 hours after drug-treatment.

Inhibition of Fibronectin secretion is physiological and the determination of its quantity is based on the following criteria:

1. Fibronectin is secreted from viable cells. Only cell with over 85% viable cells after drug-treatment are employed in these experiments. The viable cells were determined by MTT assay.

2. For comparison, the immuno-band intensity from each samples are normalized with cell mass. The cell mass was determined by the MTT assay and is assigned as a MTT unit for each cell sample.

(Results of F4) Under a sub-lethal drug concentration (10 ug/ml Y), Over 95% of cells after 18 hours of Y-treatment was viable as determined by MTT assay. Western Blots show a reduction of Fibronectin secretion by cells into culture medium after Y-treatment. Scan of Fibronectin Western bands (average 6 pairs of blots) shows that there is a 40% reduction of Fibronectin secretion after 18 hours of Y-treatment.

(Results of F5) Similarly, 85% of cells after 24 hours of Y-treatment were viable as determined by the MTT assay. Western blot shows a reduction of Fibronectin bands of Y-treated samples. Based on 6 pairs of blots and after normalize them to MTT units, a 31% reduction of Fibronectin band intensity of Y-treated samples was observed. Accordingly, these results indicate that Fibronectin secretion by cells reduce 31% after 24 hours of Y-treatment.

(Results of F7) Effects of Paclitaxel on Fibronectin secretion by ES2 cells. To demonstrate that not all anticancer drugs can inhibit Fibronectin secretion from cells, we employed Paclitaxel, a well known anticancer drug that is effective for ovarian cancer. Our results showed that there is no inhibition of Fibronectin secretion with Paclitaxel treatment in ES2 cells (10 to 50 ng/ml, the IC_{50} of Paclitaxel is 1.5 ng/ml). This study also showed that Fibronectin secreted by ES2 cells reduced 30-40% after Y-treatment which agrees with previous results.

(Results of F8) In addition to ES2 cells, another human ovarian cancer cells (Hey8A) were employed in this study. It was found that Y-treated Hey8A cells secrete 31% Fibronectin as compared with the DMSO control, accordingly it has a inhibition of 69%.

Beside ovarian cancer, other human cancer cells were tested in the following experiments. These experiments show that the secretion of Fibronectin from cancer cells derived from lung, bladder, liver, brain and skin is inhibited by Xanifolia-Y treatment.

(F11) For lung carcinoma cells (H460), at concentration of 20ug/ml, there are inhibitions of Fibronectin secretion ranged from 20-60%.

(F12A) For bladder carcinoma cells (HTB-9), Xanifolia-Y (10 ug/ml) inhibits 50% of Fibronectin secretion.

(F15) In liver HepG2 cells. 10 ug/ml of xanifolia-Y inhibits 42% secretion of Fibronectin.

(F16) Incubation of brain glioblastoma T98G cells with10ug/ml of xanifolia-Y inhibits 27% Fibronectin secretion and with 20ug/ml Y inhibits74% Fibronectin secretion.

(F17) For skin SK-Mel-5 cells, the inhibition is 40-57% with 20 ug/ml of Xanifolia-Y.

Studies of xanifolia-Y analogs and other saponin on Fibronectin secretion from ES2 cells.

(F 23) To study the inhibition effect with other saponins, we tested the compound O54, a triterpenoid saponin isolated from the same plant. With O54, there is no inhibition activity of Fibronectin secretion in ES2 cells, even at higher dose of 40 ug/ml (instead of the usual effective concentration of 10 ug/ml). This result indicates there is specificity in triterpenoid saponin that is responsible for the inhibition effect.

(F21) To research for functional groups that are effective for Fibronectin inhibition activity, we tested several derivatives of xanifolia-Y3. In these experiments, ES2 cells treated with ACH-Y (Y3 without sugars) and AKOH-Y (Y3 without the C21, C22 angeloyl group).

With 20 ug/ml Ach-Y, there is a reduction of Fibronectin secretion from ES2 cells (ranging from 53% - 75% of the control). Inhibition of Fibronectin secretion was less (or not observed) when only 10 ug/ml Ach-Y was used. However, no effect was observed with AKOH even at 80 ug/ml.

(F 13) We also tested for inhibition activity with beta-Escin, a triterpenoid saponin with only one angeloyl group attached at C21.

The results show that 10 and 20 ug/ml of beta-Escin inhibit 7% and 48%, respectively, of Fibronectin secretion from ES2 cells. But 10 ug/ml of xanifolia-Y inhibits 49% Fibronectin secretion. Results indicate that beta-Escin also inhibits Fibronectin secretion but has half potency as xanifolia-Y.

(F14) (F24) We have determined the inhibition effect of different analogs of xanifolia-Y on ES2 cells. The results are shown in the following table.

ES2 cells	β-ES-10	X-10	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-20	AKOH-80
% inhibition	19	39	34	41	47	34	48	No effect

All samples (except AKOH) tested have effects of inhibition of Fibronectin secretion from ES2 cells. With 80 ug/ml of AKOH-Y which is 4 times higher concentration used in others saponins (10 ug/ml), it still has no effect on inhibition of Fibronectin secretion on ES2 cells.

In conclusion, saponins in general have effects in inhibition of Fibronectin secretion from ES2 cells. The fact that AKOH-Y (the Y3 without diangeloyl group) does not show any activity, indicating that acylation of C21, 22 positions is important for the inhibition activity.

In addition to ES2 cells, other cancer cells derived from different organs were also investigated. Results are shown in following tables.

(F25, 26, 31B) Liver

HepG2	β-ES-10	X-10	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-30
% inhibition	44	42	40	33	48	10	21

(F27,29) Lung

H460	β-ES-20	X-20	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-20
% inhibition	No effect	37	22	13	19	18	28

(F28, 30) Bladder

HTB-9	β-ES-10	X-10	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-30
% inhibition	47	38	32	50	51	60	No effect

F 31, 32) Brain

T98G	β-ES-20	X-20	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-20
% inhibition	66	52	22	40	26	24	30

(F 33) Skin

SK-MEL-5	β-ES-20	X-20	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-30
% inhibition	17	15	27	10	11	No effect	21

(F20) Determination of cellular contents and secretion of Fibronectin after xanifolia-Y-treatment

Results: This experiment shows that (1) there is a 46% reduction (54% of control) of Fibronectin secretion after xanifolia-Y-treatment and (2) the Fibronectin cellular content decrease 70% (30% of control) after the Y-treatment; (3) there is no change of the cellular beta-actin content in ES2 cells after the Y-treatment.

Up regulation of Angiopoietin 2 (Ang2) in ES2 cells with Xanifolia-Y treatment.

Meothods: ES2 (human ovarian carcinoma cells) were grew in RPMI 1640 medium. 4.5 million cells were seeded in a T75 flask and grown for 24 hours before drug-treatment.

Drug-treatment: Cells cultures were treated with 5, 10 and 15 ug/ml (final concentration) of Xanifolia-Y3 [Y3-5, Y3-10, Y3-15]. or DMSO control [D-10]. After 24 hours, cells were suspended in 1 ml of SDS sample buffer (cell-extract). Samples (80 ul/lane) were applied to 10% SDS gel and electrophoresis was conducted with 100 volts for 2 hours. Protein was transferred to a nitrocellulose membrane electrophoretically. The nitrocellulose blot was blocked with 5% non-fat dry milk in PBS. The blot was then incubated with the first antibodies (goat anti-Ang2, SIGMA A0851) and second antibody (donkey anti-goat AP conjugated, Promega V115A). The immuno-bands were developed with BCIP/NBT color development system (Promega S3771).

Results: As shown in Figure 5, a Angiopoietin-2 immuno-band (M.W,. 66K) was observed in cell extract from cells treated with 15 ug/ml Xanifolia-Y . No detectable or minimal immuno-band of Angiopoietin-2 was observed in control and low concentration of xanifolia-Y under these conditions. This results indicate that treatment of Xanifolia-Y in ES2 cells increase the cellular content of Angiopoietin-2. These results corroborate the results of Microarray studies.

This invention provides compositions and methods for modulating the gene expression in cancer cells, wherein the modulating comprises of positive and negative regulation, wherein genes being modulatated are adhesion proteins; wherein modulation includes expression, production and secretion of adhesion proteins, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, cadherin, heparin, tenascin, CD 54, CAM. This invention provides compositions and methods for modulating angiopoietins, wherein comprises positive regulating the angiopoietin 2, wherein comprises negative regulating angiopoietin 1. The composition and method of this invention comprises a triterpene wherein acylation group at carbon position 21 and/or 22 of the triterpene is necessary for the function and are selected from angeloyl, acetyl, alkanoyl, alkenoyl and acyl group. The sugar moiety (ies) at position 5 of the triterpene is important for enchancing activity of these compounds.

EXPERIMENTAL DETAILS

Experiment details of herb extraction, analysis of extract components by HPLC, determination of the cell-growth activity effected by Xanifolia Y with cells derived from different human organs using MTT Assay, purification of the bioactive components from plant extract, fractionation of plant extracts with FPLC, isolation of component Ys with preparative HPLC, determination of the chemical structure, cell experiments and aminal studings are disclosed in PCT/US05/31900, U.S. Serial No. 11/289142, U.S. Serial 10/906303, U.S. Serial No. 11/131551 and U.S. Serial Nos.11/683198, filed on March 7, 2007, PCT/US2007/077273, filed August 30, 2007, U.S. Serial No. 60/890380, filed on February 16, 2007, U.S. Nos. 60/947,705, filed on July 3, 2007, the contents of which are incorporated herein by reference.

MicroArray

Experiment 1

Analysis of gene expression of ES2 cells after Y-treatment by Microarray

In this invention, the microarray experiments were done in studying the gene expression. Total number of 54676 genes has been studied.

Cell culture and drug-treatment.: ES2 cells were seeded in a T-25 flask with 4.5 million cells per flask for 24 hours. Cell culture was replaced with fresh medium with

xanifolia-Y (Y) or DMSO no drug control (D) for 24 hours. Cells were then harvested for RNA isolation. Three experiments were done.

RNA extraction, labeling, hybridization, and data analysis. RNA was extracted from tumor cells using the Qiagen RNeasy Kit. RNA quality and quantity was checked by the Agilent BioAnalyzer and the NanoDrop® ND-1000 spectrophotometer respectively before further manipulation. The first and second cDNA strands were synthesized from 20 ng of total RNA using the Affymetrix T7 oligo(dT) primer protocol and kit for the two-cycle amplificaton. To produce amplified biotin-labeled-cRNA, the cDNA was reverse transcribed by in vitro transcription using the MegaScript kit from Ambion. 15.0 µg of the labeled cRNA was fragmented and re-checked for concentration using the NanoDrop® ND-1000 spectrophotometer. A hybridization cocktail containing Affymetrix spike-in controls and fragmented labeled cRNA was loaded onto the Human U133 Plus 2.0 GeneChip® oligonucleotide array. The Affymetrix array (Affymetrix, Inc.Santa Clara, CA) is comprised of over 1,300,000 unique oligonucleotide features that represent greater than 38,500 well-substantiated human genes. The array was hybridized for 16 hours at 45°C with rotation at 60 rpm then washed and stained with a strepavidin, R-phycoerythrin conjugate stain on the Affymetrix Fluidicis Station 450. Signal amplification was done using biotinylated antistreptavidin. The arrays were scanned using the GeneChip® 3000 confocal laser scanner with autoloader. The images were analyzed and quality control metrics recorded using Affymetrix GCOS software version 1.4. Lastly, the expression value for each gene was calculated using dChip PM-only model based or Plier algorithm.

Data Analysis Methods

Pairwise comparisons were made as follows: Treated vs. Control (Y vs. D), Modified Drug vs Control (YM/ACY-H vs. D) and Treated vs. Modified Drug (Y vs. YM/ACH-Y) Cel files analyzed using the Bioconductor package of R Statistical programming. Limma analysis generated a reasonable number of changing genes between the samples.

The raw data in the .CEL files were normalized by the GCRMA method (robust multi-array analysis). It is implemented in Bioconductor (http://www.bioconductor.org/). The raw signal intensity data were normalized, background corrected and

summarized based on certain statistical models, and an expression value, **in log2-scale**, is obtained per chip per probe set. Then the null hypothesis was tested that there's no significant changes in gene expression between the treatment pairs. This was done by LIMMA and is also implemented in Bioconductor. It uses empirical Bayes method to estimate the variance in gene expression. One comparison was made, namely, High Grade vs. Low Grade. The raw p-values were adjusted by the Benjamnin-Hochberg method for false discovery rate (FDR) control. All data sets contained a significant number of genes with a p-value less than 0.05, which is that the probability that a gene is NOT differential expressed (false positive) is 1:20.

All expression data is filtered by p-value (0.05).

The raw p-values were adjusted by the Benjamnin-Hochberg method for false discovery rate (FDR) control to yield an adjusted p-value.

Results: Please see Table 1 to 12

Inhibition of Fibronectin Secretion by Xanifolia-Y (Western blot)

Experiment 2 (F1)

Methods:

Cells: ES2 cells were grew in T-25 flask with RPMI 1640 medium over night before drug-treatment.Drug-treatment: cells cultures were replaced with fresh RPMI medium with Xanifolia-Y (10 ug/ml final concentration) or DMSO (as control) at 0 hour.At 1, 2, 4, 8 and 24 hour, aliquot of culture medium was taken out for Fibronectin determination. Fibronectin was determined by Western blot with monoclonal antibody (SIGMA) specific to human Fibronectin only.

Results (also see Figure 1):

1. Cells treated with DMSO (as no drug control) secret Fibronectin to medium and the amount of Fibronectin accumulated with time. There is no or only minimally secretion of Fibronectin observed in cell culture treated with Xanifolia-Y.
2. For controls, Fibronectin immunoband was not observed in RPMI medium with fetal bovine serum, or employing the normal mouse serum (NS1).

Experiment 3 (F3)

Methods:

Cells: ES2 cells were grew in RPMI 1640 medium over night before drug-treatment. Drug-treatment: cells cultures were replaced with fresh RPMI medium containing Xanifolia-Y (10 ug/ml final concentration) or DMSO (as control) at 0 hour. At 4 hours (A) or 8 hour (B), culture medium was replaced with fresh culture medium without drug. At 2, 4, 8 and 24 hour, aliquot of culture medium was taken out for Fibronectin determination. Fibronectin (FN) was determined by Western blot with monoclonal antibody (SIGMA) specific only to human Fibronectin.

Results (also see Figure 2):

(1) Compare the control and Y-treated cells before drug removal (at 4 and 8 hours), there is a reduction of FN secretion from Y-treated cells. There is no obvious cell morphology change during these times, suggesting cells are alive.

(2) Compare the control and Y-treated cells after the removal of drug at 24 hours, it was estimated that secretion of FN from Y-treated cells was reduced to over 50%.

(3) The amount of FN secreted by Y-treated cells at 24 hours is higher than those at 8 hours (before removal of Y) indicating that cells are still alive after Y-treatment.

Experiment 4 (F4)

Methods:

Cells: ES2 cells were grew in RPMI 1640 medium over night before drug-treatment. Drug-treatment: cells cultures were replaced with fresh RPMI medium containing Xanifolia-Y (10 ug/ml final concentration) or DMSO (as control) at 0 hour. At 2, and 18 hour, aliquot of culture medium was taken out for Fibronectin determination (Western blot method). Cell viability at 18 hours was determined by MTT assay. Cultures were replaced with RPMI medium with MTT and incubated for an hour. The formation of formazan was dissolved in DMSO and OD at 570nm was measured.

Results (also see Figure 2):

- Over 95% of cells after 18 hours of Y-treatment were viable as determined by MTT assay.
- Western Blots show a reduction of FN secretion by cells into culture medium after Y-treatment. Scan of FN Western bands (average 5 sets of blots) shows that there is a 40% reduction of FN secretion after 18 hours of Y-treatment.

Experiment 5 (F5):

Methods:

Cells and Drug-treatment: same as previous experiments. After 7 or 24 hours, aliquot of culture medium was taken out for Fibronectin determination (Western blot method). Cell viability at 24 hours was determined by MTT assay.

Results:

- 93% and 85% of cells after 7 and 24 hours, respectively, of Y-treated cells was viable as determined by MTT assay.
- Change in Fibronectin secretion during the first 7 hours of Y-treatment is not noticeable. However, after 24 hours, as compared with the control, the Fibronectin band of Y-treated samples is reduced. Based on same amount of live cells, the intensity of the immuno-bands were compared (per MTT O.D. unit). The scan of 3 pairs of blots shows a 31% reduction of Fibronectin band. Accordingly, these results indicate that Fibronectin secretion by cells reduce 31% after 24 hours of Y-treatment.

Experiment 6 (F 7): Effects of Paclitaxel on Fibronectin secretion by ES2 cells

Methods:

Cells: ES2 cells were grew in RPMI 1640 medium over night before drug-treatment.

Drug-treatment: cells cultures were replaced with fresh RPMI medium containing DMSO (as control) [D]; Xanifolia-Y (10 ug/ml) [Y]; or Paclitaxel 10 or 50 ng/ml [T10, ro T50]. After 24 hours, aliquot of culture medium was taken out for Fibronectin determination (Western blot method). Cell viability at 24 hours was determined by MTT assay.

Results:

Based on the MTT units (cell basis) of treated cells and compared those with the DMSO control, 87%, 94% and 91% growth of Y, T10 and T50 cells, respectively, were viable after 24 hours of treatment.

The amount of Fibronectin secreted by cells into medium was determined by Western blot assay. The amount of Fibronectin secreted per cells basis was determined by dividing the Western-band intensity with the MTT unit.

By comparing with the DMSO control, ES2 cells treated with 10 ng/ml or 50 ng/ml Taxel secret 105% or 97%, respectively, of Fibronectin into medium during 24 hours of treatment. At the same time, Y-treated ES2 cells secreted 62% of control (a reduction of 38%).

Experiment 7 (F 8): Hey8A cells treated with Xanifolia-Y

Methods:

Cells: Hey8A (human ovarian carcinoma cells) were grew in RPMI 1640 medium to 90% confluent before drug-treatment. Drug-treatment: Cells cultures were replaced with fresh RPMI medium containing either DMSO (as control) [D1]; or Xanifolia-Y (10, 15, or 20 ug/ml) [Y1, Y2 and Y3]. Aliquot of medium was removed as 0 hours sample and no FN was detected at this time. After 24 hours, aliquot of culture medium was taken out for Fibronectin determination (Western blot method). Cell viability at 24 hours was determined by MTT assay. Cultures were replaced with RPMI medium (5 ml) with MTT and incubated for an hour. The formation of formazan was dissolved in DMSO and OD at 570nm was measured.

Western Blot: Spent culture medium (0.6 ml) was mixed with SDS sample buffer (0.2 ml), boiled for 3 minutes before loading to SDS gel. Samples (60 ul/lane) were applied to a 6% SDS gel and electrophoresis was conducted with 100 volts for 2 hours. Protein was transferred to a nitrocellulose paper electrophoretically (30 min at 100 volts). The Western blot was incubated with the first antibody (mouse anti-FN, specific to human FN, SIGMA F0916) and second antibody (Anti-mouse IgG AP conjugated, Promega S3721). The immunobands were developed with BCIP/NBT color development system (Promega S3771).

Results:

- After 24 hours of drug-treatment, cells with 15ug/ml and 20ug/ml were found dead (floating) and were not further proceeded. Cells with DMSO and 10 ug/ml Y were processed.
- The MTT assay showed that the growths of cells with Y-treatment (10ug/ml) are 83% of control.
- The Western blot show that the band intensity of Y-treated samples (Y1) is much reduced compare to the DMSO control (D1)
- The average band intensity after corrected with the MTT unit are: 1179 and 366, for DMSO control and Y-treated samples, respectively. Accordingly, Y-treated Hey8A cells secrete 31% Fibronectin (FN) as compared with the DMSO control, or a 69% inhibition.

Experiment 8 (F 11): Inhibition of Fibronectin secretion by Xanifolia-Y in Human Lung Carcinoma cells (H460)

Methods: please see Experiment 8.

Results: Lung cells (H460) are sensitive to Y in inhibition of FN secretion. Based on MTT results, cells are still viable at 20 ug/ml Y, but the inhibition of FN is over 60%.

Experiment 9 (F 12): Inhibition of Fibronectin secretion by Xanifolia-Y in bladder Carcinoma cells (HTB-9)

Methods: please see Experiment 8.

Results:

- The MTT assay showed that the growth of cells treated with 10 ug/ml Y reduced to 77% - 91% compared to the DMSO control.
- The Western blot shows that the FN band intensity of Y-treated samples are reduced. After corrected with the MTT unit (equivalent to cell mass) there is about 50% reduction of FN band intensity per cell mass.
- These results indicate that Xanifolia-Y (10 ug/ml) inhibit 50% of FN secretion.

Experiment 10 (F 13): ES2 cells treated with Y and beta-Escin

Methods: please see Experiment 8

Results:

- The MTT assay showed that the growth of cells with Y, Es10 and Es20 are 89%, 90% and 82%, respectively as compared to the DMSO control.

- The Western blot show that the FN band intensity of Es10 and Es20 samples are 93% and 52%, respectively, of DMSO control. The band intensity of Y10 sample is 51% of control.

- These results show that 10 and 20 ug/ml of beta-escin inhibit 7% and 48%, respectlvely, of FN secretion. But 10 ug/ml of Y inhibits 49% FN secretion.
- Results indicate that beta-escin also inhibits FN secretion but with half potency as Xanifolia-Y.

Experiment 11 (F 14): ES2 cells treated with different Xanifolia-Ys

Methods: please see Experiment 8

- Two experiments were done (FN14B and FN14C). Five gels per each experiment were run.

Results:

Except for AKOH-Y (the Y3 without diangeloyl group), all samples have some degrees of inhibition of FN secretion from ES2 cells. 80 ug/ml of AKOH-Y which is 4 times higher concentration used in others saponins (10 ug/ml), still have no effect on inhibition of FN secretion on ES2 cells.

ES2 cells	β-ES-10	X-10	Y1-10	Y3-10	Y7-10	AKOH-80
% inhibition	19	39	41	47	34	No effect

Conclusion:

It seems that saponins in general have effects in inhibition of Fibronectin secretion from ES2 cells. However, this experiment found that acylation of C21, 22 positions is important for the inhibition activity.

Experiment 12 (F 23): ES2 cells treated with O54

Methods: Please see Experiment 8.

Results: Based on these results, there is no inhibition of FN secretion in ES2 cells with O54 treatment at 40 ug/ml.

Experiment 13 (F 24): ES2 treated with Y0 and Y5

Methods: please see Experiment 8.

Results: By comparing the immuno band's intensities of these samples the results of this experiment indicate that: (1) Y5 has same activity as Y3 for inhibition of FN secretion (both inhibit 68% at 10 ug/ml);

(2) Y0 is weaker as compare to Y3 for inhibition of FN secretion.(inhibit 34% at 10 ug/ml);

(3) Conclusion, both Y0 and Y5 have inhibition activity for FN secretion from ES2 cells.

Experiment 14 (F 25, 26): HepG2 cells treated with Ys

Methods: Please see Experiment 8.

Results: By comparing the immuno band's intensities of these samples (see table), it was found that at concentration of 10 ug/ml. X, ES, Y0, Y1, Y3, and Y5 have inhibition effect on Fibronectin secretion from HepG2 cells. Minimum or No effect was observed with Y7, Ach (10 ug/ml) and AKOH (80 ug/ml).

HepG2	β-ES-10	X-10	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-30
% inhibition	44	42	40	33	48	10	21

Experiment 15 (F 27, 29): NCI-H460 cells (Lung) treated with Ys

Methods: please see Experiment 8

H460	β-ES-20	X-20	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-20
% inhibition	No effect	37	22	13	19	18	28

Experiment 16 (F 28, 30): HTB-9 cells (bladder) treated with Ys

Methods: please see Experiment 8

(FN28, 30) Bladder

HTB-9	β-ES-10	X-10	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-30
% inhibition	47	38	32	50	51	60	No effect

Experiment 17 (F31, 32): T98G (brain) treated with Y2

Methods: please see Experiment 8

TG98G	Y0-10	Y1-10	Y3-10	Y7-10	X-20	ES-20	ACH-20
% inhibition	22	40	26	24	52	66	30

Experiment 18(F 33): SK-MEL-5 cells treated with Ys

Methods: please see Experiment 8

SK-MEL-5	β-ES-20	X-20	Y0-10	Y1-10	Y3-10	Y7-10	ACH-Y-30
% inhibition	17	15	27	10	11	No effect	21

Experiment 19(F 20): Determination of cellular contents and secretion of FN after Y3-treatment

Methods:

Cells: ES2 (human ovarian carcinoma cells) were grew in RPMI 1640 medium. 1.5 million cells were seeded in a T25 flask and grown for 24 hours before drug-treatment. Drug-treatment: Cells cultures were replaced with fresh RPMI medium containing either 2.5 ul of DMSO (as control) [D]; or 10 ug/ml (final concentration) of Xanifolia-Y3 [Y]. After 24 hours, aliquot of culture medium was taken out for Fibronectin determination (Western blot method). The attached cells were suspended in 1 ml of SDS sample buffer (cell-extract).

Western Blot: Spent culture medium (0.6 ml) was mixed with SDS sample buffer (0.2 ml), and the cell-extract was boiled for 3 minutes before loading to SDS gel. Samples (80 ul/lane) were applied to a 6% - 10% SDS gel and electrophoresis was conducted with 100 volts for 2 hours. Protein was transferred to a nitrocellulose membrane electrophoretically (30 min at 100 volts). The nitrocellulose blot was blocked with 5% non-fat dry milk in PBS (1-2 hours). The blot was then incubated with the first antibodies (mouse anti-FN, specific to human FN, SIGMA F0916 and mouse anti-beta actin, SIGMA A5316) and second antibody (Anti-mouse IgG AP conjugated, Promega S3721). The immuno-bands were developed with BCIP/NBT color development system (Promega S3771). Determination of Western band intensity: The band-images of Western blot were captured with a digital camera (3-5 pictures were taken per gel) and the intensity of bands was determined using "Image J" software.

FN concentrations were normalized with the cellular beta-Actin concentrations. Fibronectin secreted into medium and inside Y-treated cells were determined and compare to controls (DMSO-treated cells).

Results: This experiment shows that (1) there is a 46% reduction (54% of control) of FN secretion after Y-treatment and (2) the FN cellular content decrease 70% (30% of control) after the Y-treatment; (3) there is no change of cellular beta-aecin concentration after the Y-treatment.

Experiment 20: Animal Study

- Athymic Nu/Nu mice (2-3 months old) were transplanted sc with ES2 (human ovarian cancer) cells.
- Five days after the transplant (day one), mice were divided into two groups (H and J) with two animals in each group.
- Group H: On days 1-5, and 8-10 mice received daily drug administration of Xanifolia-Y, by i.p. route at dose of 2.5 mg/kg.
- Group J mice received no drug-treatment.

Result:

Group H: Mice received drug-treatment, tumor size is 10 mm in 10 days

Group J: Mice received no drug-treatment, tumor size is 18 mm in 10 days

The tumor size is 45% smaller in mice with drug than the mice with no drug in 10 days period.

Experiment 21: Aminal Study

Methods

- Athymic Nu/Nu mice (5-6 weeks old) are divided into three groups (O, P and Q) with 5-6 animals in each group.
- On day 0, all mice were transplanted intra-peritoneally with ES2 (human ovarian cancer) cells.
- Group O: animals received no drug-treatment.
- Group P: On days 4-8, 11-15, 18-22, 25-29, 32-36,39-43, animals received daily drug administration of Xanifolia-Y, by i.p. route at dosage of 2.5 mg/kg
- Group Q: On days 10-15, 18-22, 25-29, 32-36, 39-43, animals received daily drug administration of Xanifolia-Y, by i.p. route at dosage of 2.5 mg/kg.

Result:

The median survival time of tumor bearing mice without drug-treatment is 24 days. The median survival time of tumor bearing mice with drug-treatment starting on day 4 after tumor inoculation is 58 days (extension of life span of 141%); and The median survival time of tumor bearing mice with drug-treatment started on day 10 after tumor inoculation is 31 days (extension of life span of 29%).

Experiment 22: Inhibition of cell adhesion by Xanifolia-Y.

Methods and Results: ES2 or Hey8A cells were plated in T25 flasks with medium containing 5 ug/ml of Xanifolia-Y. Cultures were incubated for 5 hours. Attached cells were removed from flasks by trypsinization and the amounts were counted. Compare to no drug controls, 86 ± 4 % of ES2 cells and 67 ± 8 % of Hey8A cells were found attached to flasks under this condition. At 5 ug/ml Xanifolia-Y, over 90% of unattached cells are alive as determined by the trypan Blue exclusion assay and by their ability to re-attach to flasks when plating in medium without Xanifolia-Y. However, with 10 ug/ml Xanifolia-Y, less than 40% of cells attached to flasks and many of them are dead cells. This experiment shows that Xanifolia-Y inhibits cells adhesion process.

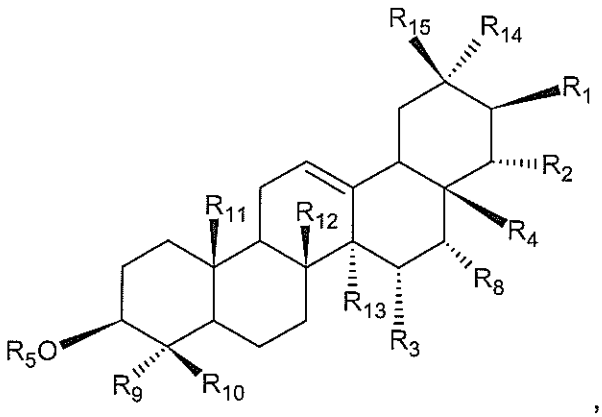
Experiment 23: Increase Synthesis of Angiopoietin-2 in ES2 cells by Xanifolia-Y

Meothods: ES2 (human ovarian carcinoma cells) were grew in RPMI 1640 medium. 4.5 million cells were seeded in a T75 flask and grown for 24 hours before drug-treatment. Drug-treatment: Cells cultures were treated with 5, 10 and 15 ug/ml (final concentration) of Xanifolia-Y3 [Y3-5, Y3-10, Y3-15]. or DMSO control [D-10]. After 24 hours, cells were suspended in 1 ml of SDS sample buffer (cell-extract). Samples (80 ul/lane) were applied to a 10% SDS gel and electrophoresis was conducted with 100 volts for 2 hours. Protein was transferred to a nitrocellulose membrane electrophoretically. The nitrocellulose blot was blocked with 5% non-fat dry milk in PBS. The blot was then incubated with the first antibodies (goat anti-Ang2, SIGMA A0851) and second antibody (donkey anti-goat AP conjugated, Promega V115A). The immuno-bands were developed with BCIP/NBT color development system (Promega S3771).

Results: As shown in this Western Blot, a Angiopoietin-2 immuno-band was observed in extract from cells treated with 15 ug/ml Xanifolia-Y. No or minimal immuno-band of Angiopoietin-2 was observed in control and low concentration of xanifolia-Y. This result indicates that treatment of Xanifolia-Y in ES2 cells increase the cellular content (or synthesis) of Angiopoietin-2. These results corroborate the results of Microarray studies.

What is claimed is:

1. A composition for modulating adhesion protein or angiopoietin, wherein the composition comprises an isolated, purified or synthesized compound, or its salt, or ester thereof, selected from the formula



, wherein

R1 is selected from hydrogen, hydroxyl, O-acetyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl and O-sugar moiety, wherein the sugar moiety substituted with two groups selecting from benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, and derivatives thereof;

R2 is selected from hydrogen, hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and O-sugar moiety, wherein the sugar moiety substituted with two groups selecting from benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, and derivatives thereof;

R4 is selected from CH_2R6 and COR6, wherein R6 comprises a group selected from hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof;

wherein at least one of R1, R2 and R6 is selected from O-angeloyl, O-tigloyl, O-senecioyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof;

R3 is H or OH; R8 is H or OH;

R5 is a hydrogen or sugar moiety(ies), wherein the sugar moiety(ies) is/are selected from a group consisting of glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose,

talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, and derivatives or combination thereof; wherein R9, R10, R11, R12, R13, R14, R15 of the compound is independently attached a group selecting from CH_3, CH_2OH, CHO, COOH, COO-alkyl, COO-aryl, COO-heterocyclic, COO-heteroaryl, CH_2Oaryl, CH_2O- heterocyclic, CH_2O-heteroaryl, alkyls, hydroxyl, acetyl group, preferably CH_3.

2. The composition of claim 1, wherein at least one of R1 and R2 is selected from O-acetyl, O-angeloyl, O-tigloyl, O-senecioyl, O-dibenzoyl, and O-benzoyl, or at least one of R1 and R2 is a sugar moiety substituted with two groups selecting from acetyl, angeloyl, tigloyl, senecioyl, dibenzoyl, benzoyl; R5 is a hydrogen or sugar moiety(ies), wherein the sugar moiety(ies) is/are selected from a group consisting of glucose, galactose, arabinose and derivatives thereof, wherein the derivatives are acid, ester and salt.

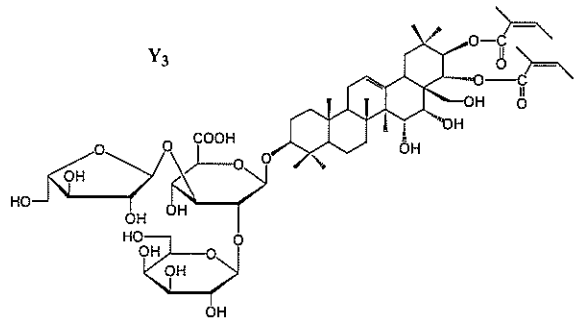
3. The composition of claim 1, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, polyglycans, cadherin, heparin, tenascin, CD 54 and CAM; wherein the modulating comprises reducing, inhibiting and stimulating.

4. The composition of claim 1, wherein modulating adhesion protein comprises reducing the fibronectin for inhibiting the metastasis or growth of cancer cells, wherein the cancer is selected from breast, leukocyte, liver, ovarian, bladder, prostate, skin, bone, brain, leukemia cancer, lung, colon, CNS, melanoma and renal cancer.

5. The composition of claim 1, wherein the angiopoietin comprising angiopoietin1, angiopoietin 2, angiopoietin 3, angiopoietin 4, angiopoietin 5, angiopoietin 6 and angiopoietin 7; wherein the angiopoietin comprising angiopoietin-like 1, angiopoietin-like 2, angiopoietin -like 3, angiopoietin-like 4, angiopoietin-like 5, angiopoietin-like 6 and angiopoietin-like 7; wherein the modulating comprises positive and negative regulating; wherein modulating angiopoietin comprises stimulating the angiopoietin 2 in order to inhibit angiogenesis; wherein modulating angiopoietin comprises inhibiting the angiopoietin 1 in order to inhibit angiogenesis; wherein modulating angiopoietin comprises inhibiting the angiopoietin-like 1; wherein modulating angiopoietin comprises inhibiting the angiopoietin-like 4.

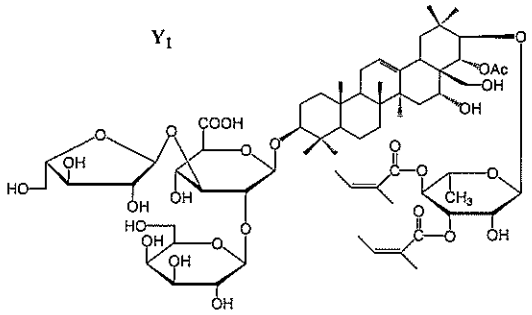
6. The composition of claim 1, wherein the compound is selected from the following:

a) An isolated, purified or synthesized compound is having structure Xanifolia(Y),



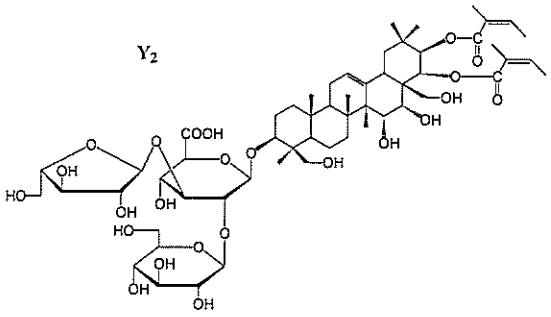
or chemical name: 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosy (1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene;

b) An isolated, purified or synthesized compound is having structure Xanifolia (Y1),



or chemical name: 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3,4-diangeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene;

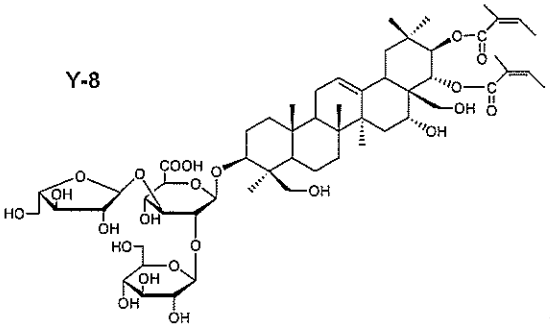
c) An isolated, purified or synthesized compound is having structure Xanifolia (Y2),



or chemical name: 3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosy (1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 24β, 28-heptahydroxyolean-12-ene;

d) An isolated, purified or synthesized compound is having structure Xanifolia (Y8),

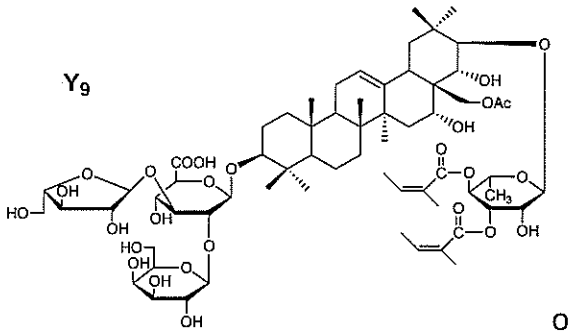
Y-8



or chemical name: 3-*O*-[β-glucopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21, 22-*O*-diangeloyl-3β, 16α, 21β, 22α, 24β, 28-hexahydroxyolean-12-ene;

e) An isolated, purified or synthesized compound is having structure Xanifolia (Y9),

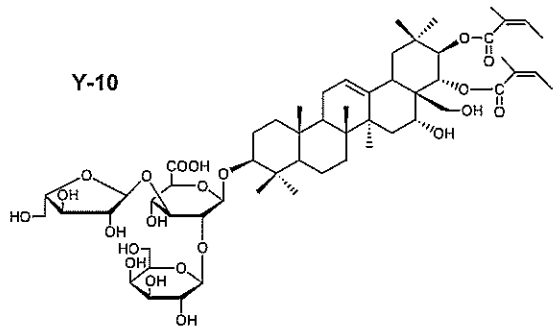
Y_9



or chemical name: 3-*O*-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21-*O*-(3,4-diangeloyl)-α-rhamnopyranosyl-28-*O*-acetyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene; and

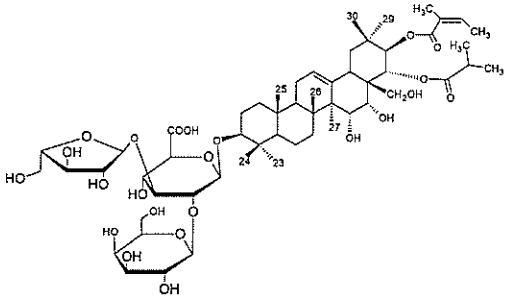
f) An isolated, purified or synthesized compound is having structure Xanifolia (Y10),

Y-10



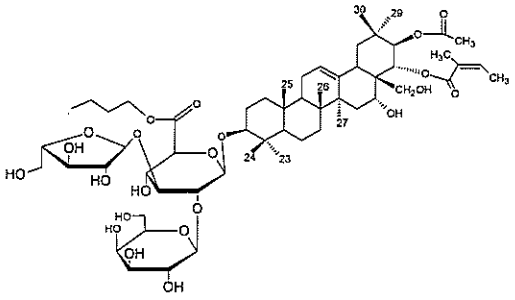
or chemical name: 3-*O*-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21, 22-*O*-diangeloyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene.

g) An isolated, purified or synthesized compound is having structure Xanifolia (Y0),



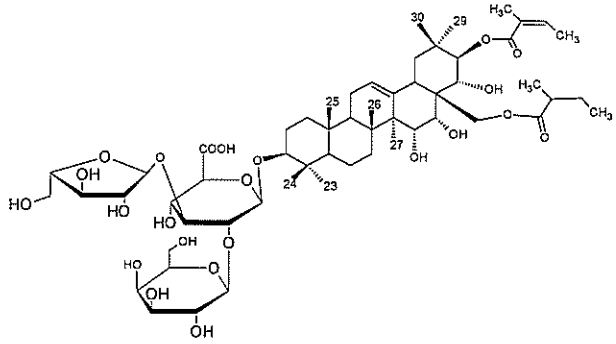
or chemical name: 3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-angeloyl, 22-O-(2-methylpropanoyl)-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

h) An isolated, purified or synthesized compound is having structure Xanifolia (X),



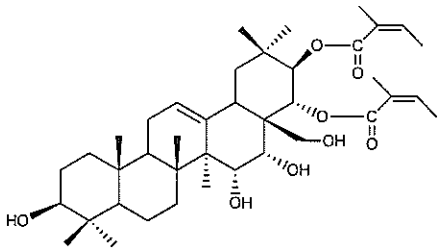
or chemical name: 3-*O*-{[*β*-D-galactopyranosyl (1→2)]-[*α*-L-arabinofuranosyl (1→3)]- *β*-D-glucuronopyranoside butyl ester}-21-*O*-acetyl-22-*O*- angeloyl- 3*β*,16*α*,21*β*,22*α*,28-pentahydroxyolean-12-ene.

i) An isolated, purified or synthesized compound is having structure (Y7),

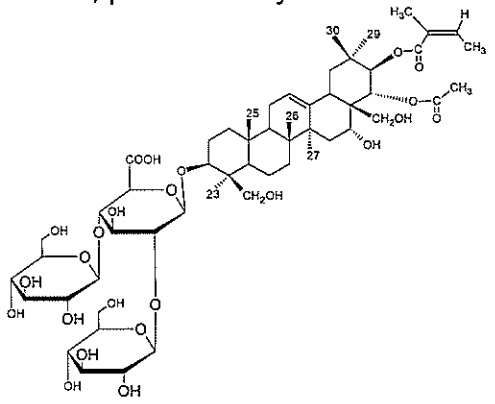


or chemical name: 3-*O*-[*β*-D-galactopyranosyl-(1→2)]-*α*-L-arabinofuranosyl-(1→3)-*β*-D--glucuronopyranosyl-21-*O*-angeloyl-28-*O*-2-methylbutanoyl-3*β*, 15 *α*, 16*α*, 21*β*, 22*α*, 28-hexahydroxyolean-12-ene

j) An isolated, purified or synthesized compound is having structure(ACH-Y):



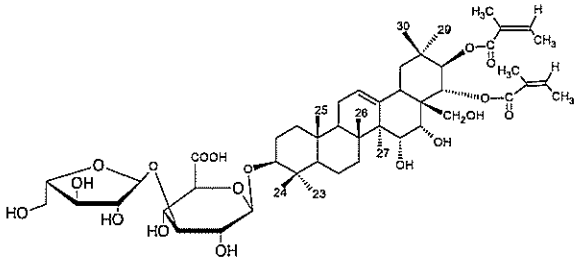
k) An isolated, purified or synthesized compound is having structure:



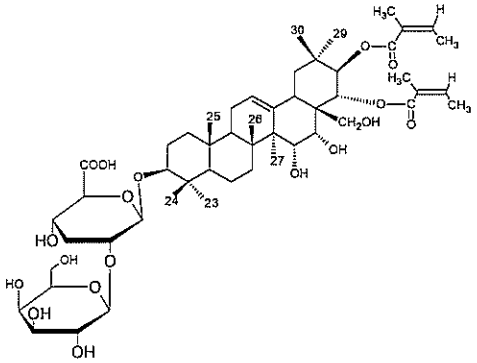
or chemical name:

3-*O*-[β-glucopyranosyl (1→2)]- β-arabinofuranosyl (1→4)-β- glucuronopyranosyl -21-*O*-angeloyl-22-O-acteyl-3β, 16α, 21β, 22α, 24β, 28-hexahydroxyolean-12-ene;

l) An isolated, purified or synthesized compound is having a structure:

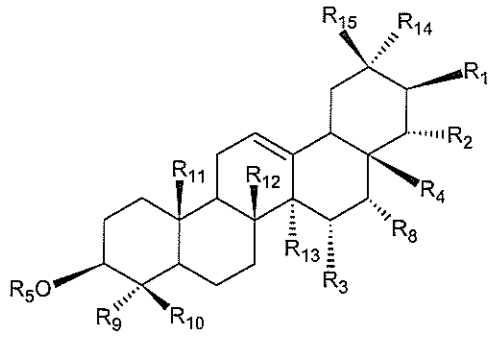


m) An isolated, purified or synthesized compound is having a structure:



7. A use of a compound for the manufacture of a medicament for modulating adhesion protein or angiopoietin in cells comprising contacting said cells with an effective

amount of an isolated, purified or synthesized compound, or its salt, or ester thereof, selected from the formula



,

wherein R1 is selected from hydrogen, hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl and O-sugar moiety, wherein the sugar moiety substituted with two groups selecting from benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, and derivatives thereof;

R2 is selected from hydrogen, hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and O-sugar moiety, wherein the sugar moiety substituted with two groups selecting from benzoyl, alkanoyl, alkenoyl, benzoyl alkyl substituted alkanoyl, aryl, acyl, heterocylic, heteroraryl, and derivatives thereof;

R4 is selected from CH_2R6 and COR6, wherein R6 comprises a group selected from hydroxyl, O-angeloyl, O-tigloyl, O-senecioyl, O-alkyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof;

wherein at least one of R1, R2 and R6 is selected from O-angeloyl, O-tigloyl, O-senecioyl, O-dibenzoyl, O-benzoyl, O-alkanoyl, O-alkenoyl, O-benzoyl alkyl substituted alkanoyl, O-aryl, O-acyl, O-heterocylic, O-heteroraryl, and derivatives thereof;

R3 is H or OH; R8 is H or OH;

R5 is a hydrogen or sugar moiety(ies), wherein the sugar moiety(ies) is/are selected from a group consisting of glucose, galactose, rhamnose, arabinose, xylose, fucose, allose, altrose, gulose, idose, lyxose, mannose, psicose, ribose, sorbose, tagatose, talose, fructose, alduronic acid, glucuronic acid, galacturonic acid, and derivatives or combination thereof; wherein R9, R10, R11, R12, R13, R14, R15 of the compound is independently attached a group selecting from CH_3, CH_2OH, CHO, COOH, COO-alkyl,

COO-aryl, COO-heterocyclic, COO-heteroaryl, CH_2Oaryl, CH_2O- heterocyclic, CH_2O-heteroaryl, alkyls, hydroxyl and acetyl group, preferably CH_3.

8. The use of a compound for the manufacture of a medicament of claim 7, wherein at least one of R1 and R2 is selected from O-acetyl, O-angeloyl, O-tigloyl, O-senecioyl, O-dibenzoyl, and O-benzoyl, or at least one of R1 and R2 is a sugar moiety substituted with two groups selecting from acetyl, angeloyl, tigloyl, senecioyl, dibenzoyl, benzoyl; R5 is a hydrogen or sugar moiety(ies), wherein the sugar moiety(ies) is/are selected from a group consisting of glucose, galactose, arabinose and derivatives thereof, wherein the derivatives are acid, ester and salt.

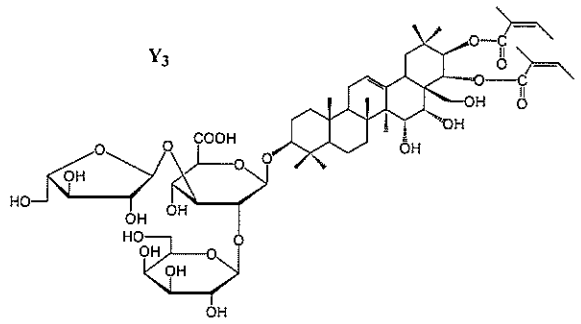
9. The use of a compound for the manufacture of a medicament of claim 7, wherein the adhesion proteins comprise fibronectin, integrins family, Myosin , vitronectin, collagen, laminin, cadherin, heparin, tenascin, CD 54, CAM; wherein the modulating comprises reducing, inhibiting and stimulating.

10. The use of a compound for the manufacture of a medicament of claim 7, wherein modulating adhesion protein comprises reducing the fibronectin for inhibiting the metastasis or growth of cancer cells, wherein the cancer is selected from breast cancer, leukocyte cancer, liver cancer, ovarian cancer, bladder cancer, prostate cancer, skin cancer, bone cancer, brain cancer, leukemia cancer, lung cancer, colon cancer, CNS cancer, melanoma cancer, and renal cancer.

11. The use of a compound for the manufacture of a medicament of claim 7, wherein the angiopoietin comprising angiopoietin1, angiopoietin 2, angiopoietin 3, angiopoietin 4, angiopoietin 5, angiopoietin 6 and angiopoietin 7; wherein the angiopoietin comprising angiopoietin-like 1, angiopoietin-like 2, angiopoietin -like 3, angiopoietin-like 4, angiopoietin-like 5, angiopoietin-like 6 and angiopoietin-like 7; wherein the modulating comprises positive and negative regulating; wherein modulating angiopoietin comprises stimulating the angiopoietin 2 in order to inhibit angiogenesis; wherein modulating angiopoietin comprises inhibiting the angiopoietin 1 in order to inhibit angiogenesis; wherein modulating angiopoietin comprises inhibiting the angiopoietin-like 1; wherein modulating angiopoietin comprises inhibiting the angiopoietin-like 4.

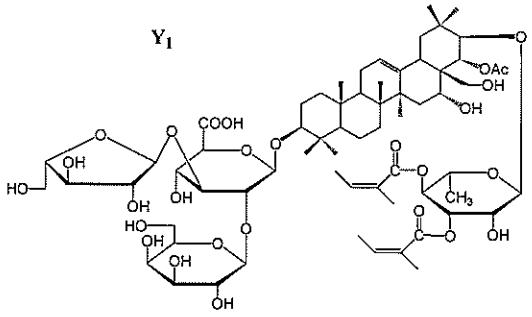
12. The use of a compound for the manufacture of a medicament of claim 7, wherein the compound is selected from the following:

a) An isolated, purified or synthesized compound is having structure Xanifolia(Y),



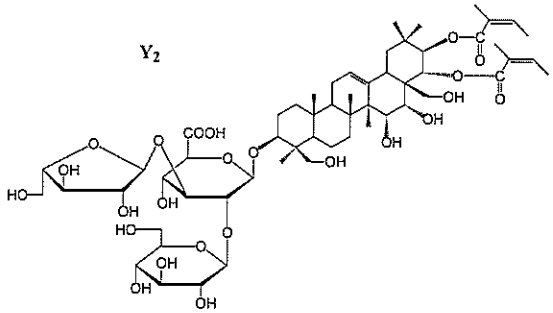
or chemical name: 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosy (1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene;

b) An isolated, purified or synthesized compound is having structure Xanifolia (Y1),



or chemical name: 3-O-[β-D-galactopyranosyl (1→2)]-α-L-arabinofuranosyl (1→3)-β-D-glucuronopyranosyl-21-O-(3,4-diangeloyl)-α-L-rhamnophyranosyl-22-O-acetyl-3β,16α, 21β, 22α, 28-pentahydroxyolean-12-ene;

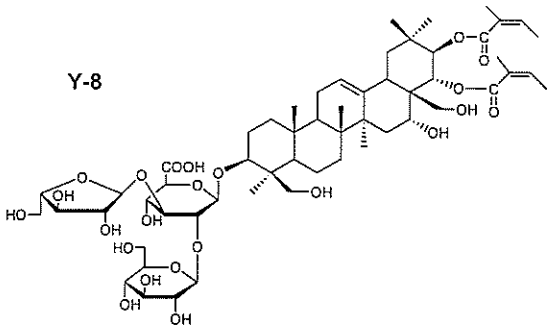
c) An isolated, purified or synthesized compound is having structure Xanifolia (Y2),



or chemical name: 3-O-[β-D-glucopyranosyl-(1→2)]-α-L-arabinofuranosy (1→3)-β-D-glucuronopyranosyl-21,22-O-diangeloyl-3β, 15α, 16α, 21β, 22α, 24β, 28-heptahydroxyolean-12-ene;

d) An isolated, purified or synthesized compound is having structure Xanifolia (Y8),

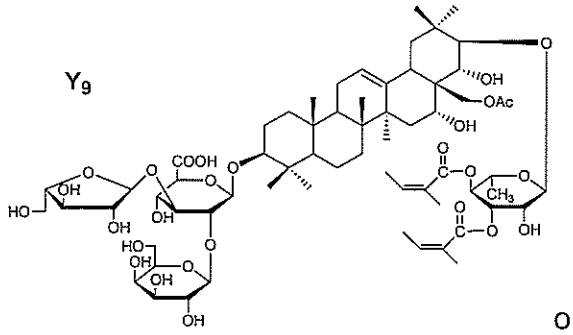
Y-8



or chemical name: 3-*O*-[β-glucopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21, 22-*O*-diangeloyl-3β, 16α, 21β, 22α, 24β, 28-hexahydroxyolean-12-ene;

e) An isolated, purified or synthesized compound is having structure Xanifolia (Y9),

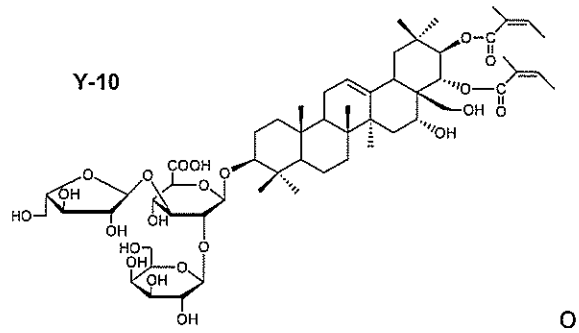
Y_9



or chemical name: 3-*O*-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21-*O*-(3,4-diangeloyl)-α-rhamnopyranosyl-28-*O*-acetyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene; and

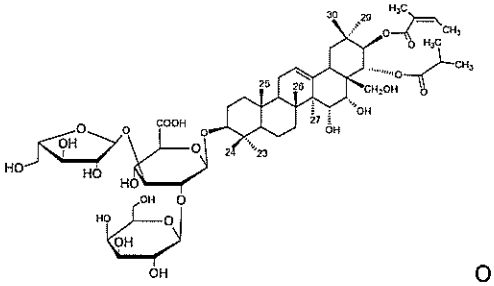
f) An isolated, purified or synthesized compound is having structure Xanifolia (Y10),

Y-10



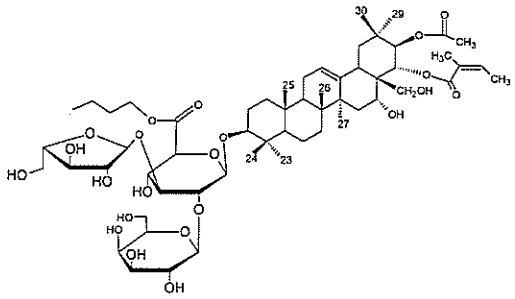
or chemical name: 3-*O*-[β-galactopyranosyl (1→2)]-α-arabinofuranosyl (1→3)-β-glucuronopyranosyl-21, 22-*O*-diangeloyl-3β, 16α, 21β, 22α, 28-pentahydroxyolean-12-ene.

g) An isolated, purified or synthesized compound is having structure Xanifolia (Y0),



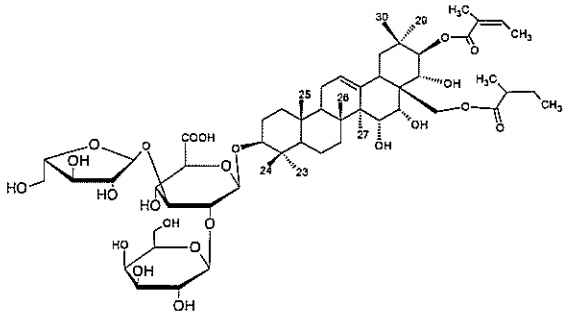
or chemical name: 3-O-[β-D-galactopyranosyl(1→2)]-α-L-arabinofuranosyl(1→3)-β-D-glucuronopyranosyl-21-O-angeloyl, 22-O-(2-methylpropanoyl)-3β, 15α, 16α, 21β, 22α, 28-hexahydroxyolean-12-ene,

h) An isolated, purified or synthesized compound is having structure Xanifolia (X),



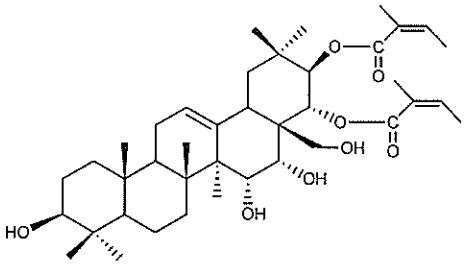
or chemical name: 3-*O*-{[*β*-D-galactopyranosyl (1→2)]-[*α*-L-arabinofuranosyl (1→3)]-*β*-D-glucuronopyranoside butyl ester}-21-*O*-acetyl-22-*O*-angeloyl- 3*β*,16*α*,21*β*,22*α*,28-pentahydroxyolean-12-ene.

i) An isolated, purified or synthesized compound is having structure (Y7),

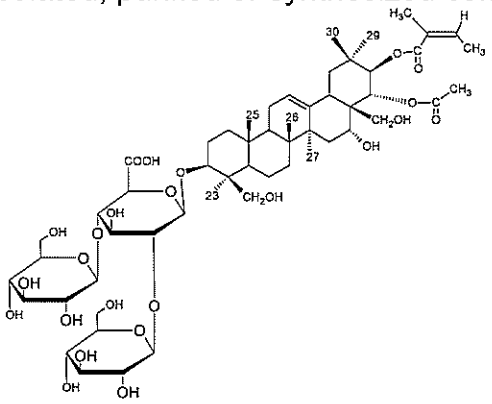


or chemical name: 3-*O*-[*β*-D-galactopyranosyl-(1→2)]-*α*-L-arabinofuranosyl-(1→3)-*β*-D--glucuronopyranosyl-21-*O*-angeloyl-28-*O*-2-methylbutanoyl-3*β*, 15 *α*, 16*α*, 21*β*, 22*α*, 28-hexahydroxyolean-12-ene

j) An isolated, purified or synthesized compound is having structure (ACH-Y):



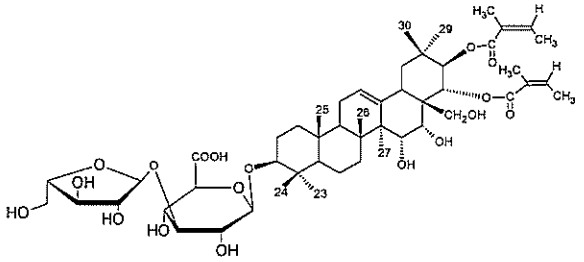
k) An isolated, purified or synthesized compound is having structure:



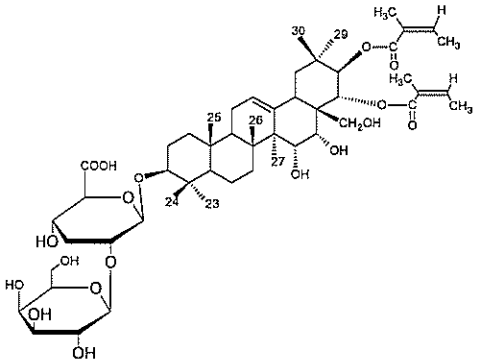
or chemical name:

3-*O*-[β-glucopyranosyl (1→2)]- β-arabinofuranosyl (1→4)-β-glucuronopyranosyl-21-*O*-angeloyl-22-O-acteyl-3β, 16α, 21β, 22α, 24β, 28-hexahydroxyolean-12-ene;

l) An isolated, purified or synthesized compound is having a structure:



m) An isolated, purified or synthesized compound is having a structure:



13. A process for administration of the composition of claim 1, wherein administration is by intravenous injection, intravenous drip, intraperitoneal injection or oral administration; wherein administration is by intravenous drip: 0.05-0.2mg/kg compound dissolved in 250ml of 10% glucose solution or in 250ml of 0.9% NaCl solution, or by intravenous injection: 0.05-0.2mg/kg/day compound dissolved in 10-20ml of 10% glucose solution or of 0.9% NaCl solution, or by intravenous drip: 0.1-0.2mg/kg/day compound dissolved in 250ml of 10% glucose solution or in 250ml of 0.9% NaCl solution, or by intravenous injection: 0.1-0.2mg/kg/day compound dissolved in 10-20ml of 10% glucose solution or of 0.9% NaCl solution, or by intraperitoneal injection(I.P.): 2.5mg/kg/day compound dissolved in 10% glucose solution or of 0.9% NaCl solution, or by oral administration wherein the dosage of mammal is 1-10mg/Kg, 10-30mg/Kg, 30-60mg/Kg, or 60-90mg/Kg compound, or by intravenous injection or intravenous drip wherein the dosage of mammal is 0.01-0.1mg/Kg, 0.1-0.2mg/Kg, 0.2 - 0.4mg/Kg, or 0.4 – 0.6 mg/Kg compound, or by intraperitoneal injection (I.P.) wherein the dosage of mammal is 1-3mg/Kg, 3-5mg/Kg, 4-6mg/Kg, or 6-10mg/Kg compound.

14. A use of a compound for the manufacture of a medicament for modulating the gene expression of cells comprising contacting said cells with an isolated, purified or synthesized compound, or its salt, or ester thereof, selected from the claim 1-6~~5~~, wherein the gene is selected from: ABL2, ADAMTS1, AKR1C3, AMIGO2, ANGPT2, ANKRD11, AP2B1, APEH, APLP2, ARL10C, ARMC4, ARMCX1, ARMCX6, ARNTL2, ARNTL2, ATF3, ATP6V0E, ATP6V1B2, ATP6V1C1, ATP6V1C1, BCL2A1, BCL6, BRI3, BTD, C14orf109, C14orf78, C17orf32, C6orf65,C9orf10, C9orf103, CAD, CAV1, CAV2, CBLL1, CCL20, CD33L3, CEBPB, CEP4, CFH /// CFHL1, CHRDL1, CITED2, CITED2, CLDN14, CLN8, CLTA, CNAP1, COG6, COL18A1, COL4A2, COL5A1, COL5A2, COL6A3, COPG, CPM, CPNE3, CPSF1, CSRP2BP, CSTB, CTNS, CXCL2, DDB1, DDIT3, DDX20, DKFZP564I1171, DKFZP586J0619, DUSP10, DUSP10, DYRK3, EEF2K, EFEMP1, EMP1, EVC, EVI2A, EXT2, FAM62A, FER1L3, FLJ14466, FLNA, FN1, FN1, GANAB, GDF15, GEM, GNPDA1, GPAA1, GPC6, GPNMB, GPNMB, GUSB, H2AFV, H2AFV, HDAC9, HDLBP, HECW2, HMGA2, HMOX1, HSDL2, HSPBAP1, HSPC196, HYOU1, IDS, IGFBP3, IKBKAP, INSIG1, IPO4, IRS2, JAG1, KDELR3, KIAA0251, KIAA0586, KIAA1211, KIAA1462, KIAA1706, KIAA1754, KRT18, KRT7, KRTAP4-7, LAMP2, LEPR, LEPREL1,

LHFPL2, LIF, LOC286044, LOC339229, LOC90693, LRRC8E, MAFG, MAGED2, MCTP1, MGC16291, MGC19764, MGC5618, MRPS30, MRPS31, MTERFD3, MYH9, NAGA, NAV2, NCSTN, NEK9, NEU1, NFKBIZ, NMT2, NPC2, NSUN5C, NTNG1, NUP188, OACT2, OS9, P4HA1, P8, PALM2-AKAP2, PALM2-AKAP2, PARVA, PBX2, PDE4DIP, PDIA4, PDIA6, PEG10, PHF19, PIK4CA, PLEKHM1, PLOD1, PLOD2, PPP1R15A, PPP1R15A, PRKDC, PRSS23, PRSS23, PSEN2, PSMD1, PTPRF, PTPRJ, RAB32, RAB9A, RG9MTD1, RGS4, RHOQ, RND3, RNF25, RNPEP /// UBE2V1 /// Kua /// Kua-UEV, RNU17D, ROBO4, RRAGC, RRS1, SEC31L1, SERPINB2, SERPINB7, SESN2, SGEF, SGSH, SKIV2L, SLC25A21, SLC35A3, SLC3A2, SMARCA1, SNAPC1, SNF1LK, SPOCD1, SPTAN1, SQSTM1, ST3GAL6, STC2, STX3A, TFPI2, TFPI2, TGFBI, TGM2, THRAP1, TLN1, TMEM60, TNFAIP3, TRIB3, TRIO, TSC2, UAP1L1, UBAP2L, UPP1, URB, USP11, USP5, VDR, WDR4, YTHDF2, ZCCHC9, ZDHHC20, ZFHX1B, ZNF185, ZNF278, ZNF690, ZNF697; or wherein the gene is selected from: FN1, ITGAV, LAMA4, LAMB2, LAMC1, LAMB1, LAMB1, LAMA4, LAMA5, LAMC1, LAMA2, LAMB1, LAMA3, SCAMP1, TICAM2, SCAMP1, TICAM2, SCAMP1, SCAMP1, CAMK2B, DL1, ICAM3,CEECAM1,ICAM5,SCAMP1, CAMK1G, CAMSAP1, MCAM, CAMTA1, CKN1, ALCAM, DCAMKL2, CEACAM3, CAMK2D, CAMK2B, SCAMP5, CAMK4, NCAM1, CAMK2G, MYH9, MYH10, MYO1D, MYO5A, MYLK, MYO6, MYO5A, MYO1C, MYLK, MYO6, MYLC2PL, MYO10, MYO6, TPM3, MYO1C, BECN1, MYO1E, TPM3, M-RIP, MYO1B, MYO10, MYO5A, M-RIP, MYO10, MYL6, MYOHD1, BECN1, TPM4, MYLK, MYH10, MYOHD1, LOC221875, LOC402643, MYO15B, LOC129285, MYH11, MYO1B, MYO1C, MYO9B, CDH13, CTNNAL1, CDH13, CDH12, CTNNB1, CDH5, CTNND1, CDH2, CTNNA1, CDH2, PCDHB16, CTNNA1, CELSR2, PCDHB6, PCDHB7, CTNND2, PCDHGC3, PCDHGB4, PCDHGA8, PCDHGA12, PCDHGC5 , PCDHGC4 , PCDHGB7, PCDHGB6, PCDHGB5, PCDHGB3, PCDHGB2, PCDHGB1, PCDHGA11, PCDHGA10 , PCDHGA9, PCDHGA7, PCDHGA6, PCDHGA5, PCDHGA4 , PCDHGA3 , PCDHGA2, PCDHGA1, CTNND1, CDH23, PCDHB12, PCDHB10, PCDH18, CDH20, PCDH9, PCDHGA12 , PCDHGA11, PCDHGA10, PCDHGA6, PCDHGA5, PCDHGA3, PCDH7, CDH18, CDH6, CCBE1, COL10A1, COL12A1, COL13A1, COL18A1, COL1A1, COL21A1, COL4A1, COL4A2, COL4A5, COL4A6, COL5A1, COL5A2, COL6A1, COL6A2, COL6A3, COL9A1, MMP9, P4HA1, P4HA2, P4HB, PCOLCE, PCOLCE2, PCOTH, PLOD1, PLOD2,

PLOD3, CIB1, ILK, ITGA2, ITGA3, ITGA4, ITGA6, ITGAV, ITGB1, ITGB1BP1, ITGB2, ITGB5, ITGBL1, TNC, EMILIN1, ICAM1, HSPG2, HPSE, HS2ST1,SDC2.

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