Title: ANTI-PROLIFERATIVE COMPOUNDS

Abstract: The present invention is based on the finding that 6-O-acyl-beta-D-glucosyl-beta-sitosterols extracted from fig latex were effective in inhibiting cell proliferation and thus may be used as anti-proliferative agents for the treatment of various diseases and disorders which correlate with undesired proliferation of cells, including cancer. Thus, the present invention provides such compounds, compositions comprising said compounds and methods of use of the compounds for inhibiting undesired proliferation of cells. The compounds of the present invention are preferably formulated for oral delivery, e.g. as a food additive.
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ANTI-PROLIFERATIVE COMPOUNDS

FIELD OF THE INVENTION

This invention concerns acylated glucosyl-β-sitosterols for use as anti-proliferative agents.

BACKGROUND OF THE INVENTION

Glucosyl-β-sitosterols as well as other glucosylsitosterols, such as stigmasterol campesterol and the like, are obtained from a variety of plant material extracts in the form of a mixture containing, in most cases, not less than 60% of glucosyl-β-sitosterols, with other glucosylsitosterols.

The biological activities of some glucosylsitosterols have been investigated such as their effects on complement activation and their anti-inflammatory activity. US 5,486,510 describes the immunomodulatory properties of mixtures of steryl glycosides including β-sitosterol glucosides (abbreviated to BSSG) and aglycone β-sitosterol (abbreviated to BSS) and further describes the in vivo effect of such mixtures in patients displaying Hashimoto’s thyroiditis, atopic exzema, psoriasis, asthma and cancer.

13:2235-2238, 1974] and have also been synthesized [Kiribuchi, T., et al., Supra, 31:1244-1247, 1967].

Fig (Ficus carica) products are widely used, both as a food and as medicine in the Middle East. The latex released on picking the fruits is used to treat skin tumors and warts [Krispil, N. in Medicinal plants – field guide to the medicinal plants of Israel (Hebrew), Jerusalem, p. 66 (1986)]. The first scientific investigation on the activity of fig latex was done by Ullman et al. in the 1940’s [Ullman, S.B., et al., J. Exp. Med. Surgery, 3:11-23, 1945; Ullman, S.B., (Supra) 10:26-49, 1952; Ullman S.B., et al., (Supra), 10:287-305]. High doses of fig latex injected into rats were found to be lethal. Smaller doses injected into mice bearing a benzpyrene-induced sarcoma caused inhibition of the growth of the tumor and even the disappearance of small tumors. The dialysate of the latex contained the active ingredient. The isolation of the active components was not pursued further, however some pharmacological work has since been reported. Fig latex was tested for its antihelmintic activity, but was found to cause acute toxicity with hemorrhagic enteritis [De-Amorin, A. et al., J. Ethnopharmacol., 64:255-258, 1999]. The leaf decoction affected lipid catabolism in hypertriglycerideremic rats [Perez, C., et al., Phytother. Res., 13:188-191, 1999] and had hypoglycemic action in type-1 diabetic patients [Serraclara, a., et al., Diabetes Res. Clin. Pract., 39:19-22, 1998].

SUMMARY OF THE INVENTION

The present invention is based on the finding that the anti-proliferative activity of fig latex extracts is attributed to acylated derivatives of glucosyl-β-sitosterols and in particular to 6-O-acyl-β-D-glucosyl-β-sitosterols (6-AGS), present in low quantities in the latex of figs.

Thus, according to a first of its aspects, the present invention concerns 6-O-acyl-β-D-glucosyl-β-sitosterols of the general formula (I):

![Chemical structure](image)

wherein said R represents an acyl group, for use as an agent for inhibiting undesired cell proliferation.

The term "**undesired cell proliferation**" as used herein, refers over proliferation of cells which correlates with a disease or disorder or with a physiologically abnormal condition. At times, undesired proliferation may also refer to proliferation of normal dividing cells such as cells of the inner lining of the intestines, cells of hair follicles and hematopoietic cells, the inhibition of which is desired in order to reduce toxic side effects of a treatment, e.g. a chemotherapeutic treatment (as will be further explained hereinafter).

The present invention also concerns composition comprising a physiologically acceptable carrier and an amount of at least one compound of the general formula (I), the amount of said compound or of a mixture of the compounds being such that when said composition is provided to an individual it is
effective for achieving a therapeutic effect, the therapeutic effect comprises inhibition of undesired cell proliferation.

The "effective amount" for purposes used herein is determined by such considerations as may be known in the art. The amount must be effective to achieve the desired therapeutic effect as described above, i.e. inhibition of undesired cell proliferation, depending, *inter alia*, on the type and severity of the disease associated with the abnormal and undesired cell proliferation and on the treatment regime. The effective amount is typically determined in appropriately designed clinical trials (dose range studies) and the person versed in the art will know how to properly conduct such trials in order to determine the effective amount. As generally known, an effective amount depends on a variety of factors including the compound/s distribution profile within the body, on a variety of pharmacological parameters such as half life in the body, on undesired side effects, if any, on factors such as age and gender, etc.

The present invention also concerns the use of at least one compound of formula (I) for the preparation of a composition, the composition comprising an amount of said compound or of a mixture of said compounds effective in achieving a therapeutic effect, the therapeutic effect comprising inhibition of undesired cell proliferation.

Yet further, the invention concerns a method for inhibiting undesired cell proliferation comprising contacting said cells with at least one compound of formula (I), as well as to a method for the treatment or prevention of a disease or disorder associated with undesired cell proliferation, the method comprising administering to a subject in need, a therapeutically or prophylactic effective amount of at least one compound of the formula (I).

The term "disease or disorder" as used herein refers to any type of disease, which is caused by, correlates or associated with abnormal and undesired proliferation of cells within the body. Non-limiting examples of such diseases
include autoimmune diseases (e.g. rheumatoid arthritis); over proliferation of skin (e.g. psoriasis); Seborrheic keratosis; papilomas; and cancer.

The term "treatment or prevention" as used herein encompass the administering of a therapeutic amount of at least one compound of the present invention which is effective to ameliorate undesired symptoms associated with a disease as defined above, to prevent the manifestation of such symptoms before they occur, to slow down the progression of the disease, slow down the deterioration of symptoms associated with the disease, to enhance the onset of remission period of the disease, slow down the irreversible damage caused in the progressive a chronic stage of the disease, to delay the onset of said progressive stage, to lessen the severity or cure the disease, to improve survival rate or more rapid recovery, as well as to prevent the disease form occurring or a combination of two or more of the above.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, a preferred embodiment will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1 shows the kinetics of the anti-proliferative activity of 6-O-acyl-β-D-glucosyl-β-sitosterols (6-AGS, 50μg/ml) on Raji cells. Raji cells were incubated in the presence (■, +6-AGS) or absence of 6-AGS (▲, -6-AGS).

Fig. 2 shows the effect of various concentrations of 6-AGS derived from fig latex (■) and of synthetic 6-PGS (▲) on proliferation of Raji cells.

DETAILED DESCRIPTION OF THE INVENTION

As detailed hereinbelow, it has now been found that acetylated derivatives of glucosyl-β-sitosterols posses an anti-proliferative activity. In particular, it has now been established that 6-O-acyl-β-D-glucosyl-β-sitosterols are effective in inhibiting proliferation of various tumor cells, including, without being limited
thereto, B-cell lymphoma, T-cell leukemia, prostate cancer and mammary cancer. Thus, the present invention provides, according to a first of its aspects, 6-O-acyl-β-D-glucosyl-β-sitosterols having the formula (I) as defined hereinbefore, for use as agents for inhibiting undesired cell proliferation.

The 6-O-acyl-β-D-glucosyl-β-sitosterols of the invention may be used in the form of substantially purified compounds or as a substantially purified mixture of said compounds, as such or in combination with other therapeutic agents (e.g. other anti-proliferating agent, immunomodulators, etc).

The acyl group may include saturated or unsaturated aliphatic chain (i.e. alkyl, alkenyl and alkynyl) and may be a branched or linear chain. Preferably, the acyl moiety contains from 2 to 30 carbon atoms and more preferably from 12 to 24 carbon atoms. According to one embodiment of the invention, the acyl moiety is a C17-acyl is selected from -(CH₂)₁₄CH₃ (palmitoyl), -(CH₂)₁₆CH₃ (stearyl), -(CH₂)₇CH=CH(CH₂)₇CH₃ (oleyl) and -(CH₂)₇CH=CHCH₂CH=CH(CH₂)₄CH₃ (linolenyl). According to one preferred embodiment, the acyl group is the palmitoyl group.

According to one preferred embodiment, the compounds of the invention are used for the treatment of various malignancies. As will be appreciated by those versed in the art, the cell division rate is a significant factor in determining the probability of a cell to become a premalignant or malignant cell. In addition, as known, the formation of a benign or malignant tumor is dependent, inter alia, on continuous divisions of the cells forming the tumor. Administration of the compounds of the invention to an individual before the formation or at early stages of the formation of a benign or malignant tumor may result in the delay or prevention of the formation of a fully-fledged tumor in the treated individual. Administration of said compounds (alone or as a mixture) to an individual suffering from a fully fledged benign or malignant tumor may result in the reduction of the tumor load in the treated individual and in the alleviation of the tumor-related symptoms. Said compound/s may be effective in the treatment of primary as well as
secondary (metastatic) tumors. Further, the compound/s may be administered in combination with one or more known treatments (e.g. chemotherapeutic agents, radiation, immunomodulators etc.) to achieve a synergistic effect. The doses of said compounds to be administered to an individual as well as the treatment modality will be dependent on characteristics of the treated individual (age, weight, medical history, etc.) as well as on characteristics of the developing or existing tumor (benign or malignant, size, origin, primary or secondary, etc.). In individuals having a high risk of developing a primary or secondary tumor, the compounds of the invention may be administered routinely in order to reduce the probability of tumor formation, however, typically, the compounds will be administered as a follow-up of an initial treatment of the primary cancer, such as chemotherapy, radiation therapy or surgery for prevention of the development of metastatic tumors.

The compounds of the invention may also be used to enhance the therapeutic index of chemotherapeutic and radiation treatments. In an individual receiving such treatments, normal dividing cells such as cells of the inner lining of the intestines, cells of hair follicles and hematopoietic cells are also harmed by the chemotherapeutic agents or radiation which are aimed at destroying the malignant cells of which a large percent are dividing cells. By administration of compounds of the invention to an individual prior to or together with such treatments, it may be possible to inhibit the proliferation of a significant percent of the normal cells. As a result, toxic side effects due to the influence of the treatments on normal cells may be significantly reduced and when beneficial, higher concentrations of the chemotherapeutic or radiation treatments may be used.

Other therapeutic applications of the compounds of the invention include inhibition of fibrosis, e.g. skin fibrosis, cirrhosis, and others. It should be noted that hitherto, fibrosis, which is an over proliferation of fibroblasts, has been treated by cytotoxic drugs, but with a limited application due to their general non-specific toxicity. Inhibition of the fibroblast proliferation by the use of the compounds of the invention provides a viable, less toxic alternative. In a similar manner, the
compounds of the invention may also be useful in the treatment of psoriasis, which results from over proliferation of keratinocytes. Seborrheic keratosis, papilomas and warts may also be treated by the compounds of the invention.

An additional phenomena which may be treated by administration of the compounds of the invention is associated with overgrowth of hair in various parts of an individual's body, such as arms, back, etc. (Hirsutism). Such undesired overgrowth of hair appears many times in aging individuals and, at times, is associated with loss of scalp hair in the same individual. Due to their ability to reduce cell growth, compounds of the invention may be useful in reducing such undesired overgrowth of hair.

As will be shown in the following examples, the compounds of the invention are effective as anti-proliferating agents, irrespective of whether they are isolated directly from figs (the naturally occurring product) or as a synthetic product and are preferably used as a food additive/supplementary to food.

When derived directly from fig latex extract, the compounds are generally obtained by filtering fig latex under conditions which allow the isolation of an aqueous filtrate from polymeric material present in said latex, for example, by suction filtration; collecting the aqueous filtrate, and treating the aqueous filtrate to obtain a compound of formula (I) or a mixture of compounds of formula (I). The treatment of the aqueous filtrate obtained following removal of the polymeric material may include additional filtrations through suitable filters, additional extractions with organic solvents such as petroleum ether, ethyl acetate, methanol; chromatography (gel filtration chromatography, high pressure liquid chromatography (HPLC), thin layer chromatography (TLC), etc.). The substantially purified compounds may then be dissolved in suitable organic solvents or mixtures of organic solvents, such as acetone, DMSO, ethanol, Tween-80 and cremophor for further use and processing.

The present invention also provides compositions comprising a physiologically acceptable carrier and an amount of at least one compound of the
general formula (I), the amount being such that when said composition is provided to an individual it is effective for achieving a therapeutic effect, the therapeutic effect comprises inhibition of undesired cell proliferation.

The pharmaceutically acceptable carriers employed according to the invention include, for example, vehicles, adjuvants, excipients, or diluents, which are well-known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active compounds and one which has no detrimental side effects or toxicity under the conditions of use. The additives may also be substances for providing the formulation with stability (e.g. preservatives) or for providing the formulation with an edible flavor etc.

The choice of carrier will be determined in part by the particular active agent, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention, including oral, topical, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration which are merely exemplary and should, in no way, be construed as limiting.

According to one preferred embodiment, the compounds of the invention are formulated in a form suitable for oral administration. Oral formulations can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active compound/s, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as alcohols either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include
one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

Due to the low solubility in water of the compounds of the invention, one preferred formulation includes liposomes. Accordingly, the active compounds may be encapsulated within the interior of a liposome, be exposed or present at the surface of the liposome (e.g. when the liposome forming lipid is derivatized with a polymer so as to enable the association of the compound onto the surface of the liposome), or be entrapped within the lipid bilayer of the liposome.

Liposomes suitable for use for formulating the compounds of the present invention include those composed primarily of vesicle-forming lipids. Vesicle-forming lipids, exemplified by the phospholipids, form spontaneously into bilayer vesicles in water. The liposomes can also include other lipids incorporated into the lipid bilayers, with the hydrophobic moiety in contact with the interior, hydrophobic region of the bilayer membrane, and the head group moiety oriented toward the exterior, polar surface of the bilayer membrane.

The vesicle-forming lipids are may be ones having two hydrocarbon chains, typically acyl chains, and a head group, either polar or nonpolar. There are a variety of synthetic vesicle-forming lipids and naturally-occurring vesicle-forming lipids, including the phospholipids, such as phosphatidylcholine, phosphatidylethanolamine, phosphatidic acid, phosphatidylinositol, and sphingomyelin, where the two hydrocarbon chains are typically between about 14-
24 carbon atoms in length, and have varying degrees of unsaturation. The above-described lipids and phospholipids whose acyl chains have varying degrees of saturation can be obtained commercially or prepared according to published methods. Other suitable lipids include glycolipids and sterols such as cholesterol.

Cationic lipids (mono and polycationic) are also suitable for use in the liposomes of the invention, where the cationic lipid can be included as a minor component of the lipid composition or as a major or sole component. Such cationic lipids typically have a lipophilic moiety, such as a sterol, an acyl or diacyl chain, and where the lipid has an overall net positive charge. Preferably, the head group of the lipid carries the positive charge or an amphipathic lipid, such as a phospholipid, is derivatized with a cationic peptide, such as polylysine or other polyamine lipids may be employed. For example, the neutral lipid (DOPE) can be derivatized with polylysine to form a cationic lipid.

The vesicle-forming lipid can be selected to achieve a specified degree of fluidity or rigidity, to control the stability of the liposome in the body fluids and to control the rate of release of the entrapped agent in the liposome. Liposomes having a more rigid lipid bilayer, in the gel (solid ordered) phase or in a liquid crystalline (liquid disordered) bilayer, are achieved by incorporation of a relatively rigid lipid, e.g., a lipid having a relatively high phase transition temperature, e.g., above room temperature, more preferably above body temperature and up to 80°C. Rigid, i.e., saturated, lipids contribute to greater membrane rigidity in the lipid bilayer. Other lipid components, such as cholesterol, are also known to contribute to membrane rigidity in lipid bilayer structures especially to reduce membrane free volume thereby reducing membrane permeability.

Lipid fluidity is achieved by incorporation of a relatively fluid lipid, typically one having a lipid phase with a relatively low liquid to liquid-crystalline phase transition temperature, e.g., at or below room temperature, more preferably, at or below body temperature.
The liposomes also include a vesicle-forming lipid derivatized with a hydrophilic polymer, which provides a surface coating of hydrophilic polymer chains on the inner and/or outer surfaces of the liposome lipid bilayer membranes. The outermost surface coating of hydrophilic polymer chains is effective to provide a liposome with a long blood circulation lifetime *in vivo*. Vesicle-forming lipids suitable for derivatization with a hydrophilic polymer include any of those lipids listed above, and, in particular phospholipids, such as distearoyl phosphatidylethanolamine (DSPE).

Hydrophilic polymers suitable for derivatization with a vesicle-forming lipid include polyvinylpyrrolidone, polyvinylmethylether, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyloxazoline, polyhydroxypropylmethacrylamide, polymethacrylamide, polydimethylacrylamide, polyhydroxypropylmethacrylate, polyhydroxyethylacrylate, hydroxymethylcellulose, hydroxyethylcellulose, polyethylene glycol, and polyaspartamide. The polymers may be employed as homopolymers or as block or random copolymers.

According to another aspect of the invention, there is provided the use of one or more compounds of formula (I) for the preparation of a composition, preferably a therapeutic composition comprising an amount of said compound/s effective in achieving a therapeutic effect, the therapeutic effect comprising inhibition of undesired cell proliferation. As indicated above, the compounds of the invention are preferably used as a food supplementary wherein the compounds or formulated in the form suitable for oral delivery, e.g. as a nutraceutical product.

According to yet another aspect of the invention there are provided a method for inhibiting undesired cell proliferation comprising contacting said cells with at least one compound of the following formula (I) and a method for the treatment or prevention of a disease or disorder associated with undesired cell proliferation, the method comprising administering to a subject in need, a therapeutically or prophylactic effective amount of at least one compound of the
following formula (I). To this end, undesirably proliferating cells or tissue are brought, *in situ*, into contact with the compounds of the invention where they exert their anti-proliferating effect.

The invention has been described in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation.

Obviously, many modifications and variations of the present invention are possible in light of the above teachings. It is therefore, to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described.

Following hereto are examples and descriptions of research involving the present invention.

**MATERIAL AND METHODS**

- FABMS was recorded on a Fison Autospec Q instrument.

- $^1$H and $^{13}$C NMR spectra were recorded on Brucker ARX-500 spectrometer.

- All chemical shifts are reported with respect to TMS ($\delta_H = 0$) and CDCl$_3$ ($\delta_C = 77.0$). The HPLC system consisted of a Waters 660 pump and a Waters 996 PDA detector. A HP model G1800B GCD having a 28 m x 0.25 mm i.d. x 0.25 μm film thickness crosslinked 5% HP ME siloxane column, programmed from 90 to 280°C at a rate of 5°C/min, interfaced with a HP model 5971 mass selective detector was used. Si gel 60 (Merck, 230-400 mesh) was used for column chromatography. Precoated Si gel plates (Merck, Kieselgel 60 F$_{254}$, 0.2 mm) were used for analytical TLC.
Extraction and Separation

The fig latex was collected and kept refrigerated until processed. The latex (500 ml) was filtered through Whatman No. 2 paper filter by suction filtration, separating polymeric material from the aqueous filtrate. Further purification of the filtrate was then attained by filtration using 5 μm disposable filter membrane. The clear aqueous filtrate was extracted three times in a separatory funnel with petroleum ether and then further extracted 3 times with 1000 ml portions of ethyl acetate for 1 hr at 62°C with stirring. The ethyl acetate was evaporated to dryness under vacuum. The residue was dissolved in methanol and filtered once more to eliminate remaining polymeric gum. A residue (2.2 g) was obtained after evaporation of the methanol. This residue was soluble in ethanol, thus allowing facile testing. The extract was tested for activity against several human cancerous cell lines including the Raji lymphoma cells derived from an African Burkitt's lymphoma [Adams, A., et al., Proc. Natl. Acad. Sci., 72:1477-1781 (1975)]. This cell line was selected as a bioactivity-guided fractionation assay for the isolation procedure.

The methanolic extract containing 2 g solid material was then chromatographed on silica gel columns with a binary solvent system of increasing polarity, using chloroform: methanol as eluent. The fractions were evaporated and the residues were assayed for their anti-proliferative activity. The activity was recovered principally in the fraction eluted in 3% methanol in chloroform. The active fraction (45 mg) was then subjected to gel filtration chromatography using Sephadex LH-20 and a mixture of methanol:chloroform:n-hexane (1:1:2, vol/vol/vol) as elution solvent. The fractions thus separated were tested for bioactivity and the activity was pinpointed to the relatively pure first eluting fraction. The isolated compound was further purified by precipitation from chloroform-acetonitrile mixture to give 8 mg of a white solid.
HPLC analysis

A normal-phase HPLC analysis was carried out using Absorbosphere HS silica 5U column (250 x 4.6 mm, Alttech) as a stationary phase. The analysis was run under isocratic conditions (propane-2-ol:n-hexane, 20:80 vol/vol) at a flow rate of 1.0 ml/min. The compound was dissolved in the mobile phase at concentration of 0.5 mg/ml and had a retention time of 6.57 minutes.

Assessment of anti-cancer activity

Various compounds isolated from fig latex were examined for their capacity to inhibit the growth of cancer cells in vitro. Numerous solvents were used for the solubilization of the isolated fractions, such as acetone, DMSO, ethanol, Tween-80, and cremophor. The Raji B-cell lymphoma line, derived from an African Burkitt’s lymphoma [Adams, A., et al., Proc. Natl. Acad. Sci., 72:1477-1781 (1975)] was used for routine assays for the anti-cancer activity of latex fractions. Raji cells were suspended in RPMI 1640 medium, supplemented with 20% heat-inactivated fetal calf serum, 2 mM-L-glutamine, 100 U/ml penicillin and 0.01 mg/ml streptomycin at 37°C in a 5% CO₂ humidified atmosphere. Aliquots of suspensions of lymphoma cells were dispensed at 200 μl volumes into wells of 96-well tissue culture plates at densities of 0.02 x 10⁶ cells/well.

Various concentrations of latex-derived compounds were introduced into 4 wells, and their efficacy was tested 3 days after initiation of the cultures, using the 3-(4,5-dimethylthiazol-2-yl) 2,5- diphenyl tetrazolium bromide (MTT) assay. The principle of this assay is that cells which survived following exposure to various compounds can reduce MTT to a dark colored formazan, while dead cells are incapable of doing so. The assay was performed as described previously [Carmichael, J., et al., Cancer Res., 47:936-942; Klumper, E., et al., Brit. J. Haematol., 93:903-910, 1996; and Rubinstein, L.V., et al., J. Natl. Cancer Inst., 82:1113-1118, 1990]. The inhibitory effect of various compounds was calculated as
percentage inhibition in comparison with the values obtained in untreated wells to which no compounds were added.

Synthesis of compounds

6-O-acyl-β-D-glucosyl-β-sitosterols (6-AGS) in which the acyl group was palmitoyl, stearyl, linoleyl and oleyl were prepared using a modification of the method proposed by Kiribuchi et al supra.

β-Sitosteryl-β-D-glucoside:

β-Sitosterol (10 g, 24 mmol) was dissolved in dry ether (150 ml) containing freshly precipitated silver oxide (15 g, 65 mmol) and anhydrous MgSO₄ (20 g, 166 mmol). α-Acetobromoglucose (10 g, 24 mmol) dissolved in 150 ml of dry ether was added drop wise. The mixture was stirred for 8 hours, then another portion of silver oxide was added and the resulting mixture was stirred for additional 16 hours at room temperature. Nitric acid (10%, 5 ml) was added to the mixture and filtered. The ethereal filtrate was washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo.

The residue was dissolved in hot ethanol and digested for a few minutes with an excess of aqueous sodium hydroxide. After cooling, water and CHCl₃ were added, mixed and transferred into a separatory funnel. The CHCl₃ layer was collected, dried over anhydrous sodium sulfate and evaporated. The product thus obtained consisted of a mixture of β-sitosteryl-β-D-glucoside and the original β-sitosterol. The product was separated by silica gel column chromatography (1:10 ratio), β-sitosterol was eluted using pure CHCl₃ and β-sitosteryl-β-D-glucoside was eluted by methanol CHCl₃ (5:95, vol/vol). When the glucoside was further purified by precipitation from a pyridine-ethanol mixture, 1.80 g (3.12 mmol) was obtained.

6-O-acyl-β-D-glucosyl-β-sitosterol:

β-Sitosteryl-β-D-glucoside (500 mg, 0.87 mmol) was dissolved in 5 ml dry pyridine and cooled to 4°C, acyl chlorides (240 mg, 0.87 mmol) in 3 ml dry benzene were added drop wise, and the mixture was stirred for 48 hours at 4°C.
After acidification with 10% sulfuric acid the reaction mixture was extracted with CHCl₃ dried over anhydrous sodium sulfate and evaporated in vacuo. The product thus obtained was separated by silica gel column chromatography (1:50 radio) and the desired product was eluted with methanol:CHCl₃ (3:97, vol/vol). The product was further purified by dissolving it in CHCl₃ and adding acetonitrile until precipitation occurred (266 mg, 0.33 mmol).

Using this method palmitoyl, stearyl, linoleyl and oleyl esters were prepared. IR spectra showed a strong absorption near 1705 cm⁻¹, characteristic of an ester. ¹³C spectra of these compounds showed a singlet at 173.5 ppm (O-CO-alkyl group) and HMBC spectra showed a correlation between this carbonyl singlet and the protons attached to carbon 6 of the glucose moiety, thus indicating the presence of the desired compound.

RESULTS

Fig latex is present in plant in extremely small quantities. Many procedures were examined in order to obtain a maximum yield of the active compounds from the fig resin. The optimal procedure established herein involved removal of inactive polymeric material by filtration, followed by extraction of the aqueous filtrate with various solvents. An extract, which was found to inhibit Raji cell proliferation was further chromatographed by several methods and the activity was monitored with an assay based on the proliferation of Raji cells. Ultimately a small amount of solid active material (0.002% overall yield from 500 ml resin, 0.008% of the nonaqueous material in the resin) was isolated.

The active material migrated as a single bank (Rf 0.7) on thin layer chromatography (TLC) silica plates developed with chloroform:methanol (9:1). The active material was tested for its purity by normal phase HPLC analysis using a method described in the Materials and Methods Section above. The active material was very pure (>99%).
The identity of the compounds within the active material was established by spectroscopic methods and confirmed by chemical synthesis. It was a mixture of 6-O-acyl-β-D-glucosyl-β-sitosterols, the acyl moiety consisting primarily of palmitoyl and linoleyl and minor amounts of stearoyl and oleyl.

From NMR data it was established that the 6-O-acyl-β-D-glucosyl-β-sitosterols, 6-AGS, contain a C_{29}-sterol (m/z 397, see below, and δ_{H} 0.629 s, Me-18 and 1.003 s, Me-19), a hexose unit (δ_{C} 99.6 d – an anomeric C-atom and 70.3 d, 73.6 d, 75.7 d, 76.4 d and 62.1 t indicative of C adjacent to oxygen) and a long aliphatic chain which in certain isolation batches was a saturated chain, while in others, there were double bonds (δ_{C} 126.0 – 130.2 ppm) and a –CH=CH-CH_{2}-CH=CH-group (δ_{H} 2.76 t and δ_{C} 25.6 t – a double allylic methylene) FABMS gave a major molecular ion at m/z 837 (MH), accompanied by weak higher peaks, as well as two strong fragments at m/z 696 (M-141, M-C_{10}H_{21}) and m/z 397 (100%). The molecular ion was confirmed by obtaining 22 and 38 m.u. shifts by addition of Na⁺ or K⁺, respectively, to the analyzed sample. The m/z 696 and m/z 397 peaks suggested a β-sitosterol, or an isomeric structure of the same formula, i.e. m/z 397 agrees with C_{29}H_{50}O-OH and m/z 696 agrees with loss of C_{10}H_{21} – the β-sitosterol side chain. Further NMR data was obtained from the acetylation products. This derivative was obtained by microacetylation of the compound (2 mg) with 1:1 mixture of Ac_{2}O and pyridine (0.1 ml), followed by silica chromatography. Due to the greater purity and better resolutions of the proton resonances, in the NMR spectrum, the acetylated product, a triacetate, was chosen for the final structure elucidation. The complete proton and carbon resonances assignment was achieved using 1D and 2D NMR experiments (PND and DEPT [Macmurray, T.A. Supra] C-NMR, COSY, HMQC and HMBC) (Table 1). Excellent agreement of the resonance lines of the aglycon with β-sitosterol was obtained. Furthermore, a–8 ppm downfield shift of C-3 of the acetylated compound in comparison with C-3 of B-sitosterol established the locality of the sugar unit. This suggestion was confirmed by an HMBC correlation from the anomeric proton (H-1') to C-3. Based on NMR
data, the hexose was determined to be glucose; each of the tetrahydroxyran (THP) ring protons possessing a large 8 - 9.6 Hz. axial-axial coupling constant. Furthermore, the 99.6 ppm $\beta_C$-value of C-F and the 8 Hz constant of H-1' determined the $\beta$-linkage to the sugar.

Table 1 - $^{13}C$ and $^1H$ chemical shifts of 6-AGS and 6-AGS triacetate in CDCl$_3$ at 125 Mhz and 500 MHz respectively

<table>
<thead>
<tr>
<th>#</th>
<th>6-AGS $^{13}C$</th>
<th>6-AGS triacetate $^1H$</th>
<th>#</th>
<th>6-AGS $^{13}C$</th>
<th>6-AGS triacetate $^1H$</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>37.2 (t)</td>
<td>1.03 (m), 1.84 (m)</td>
<td>25</td>
<td>29.3 (t)</td>
<td>1.70 (m)</td>
</tr>
<tr>
<td>2</td>
<td>28.2 (t)</td>
<td>1.60 (m), 1.84 (m)</td>
<td>26</td>
<td>19.0 (q)</td>
<td>0.83 (d)</td>
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<tr>
<td>3</td>
<td>80.1 (d)</td>
<td>3.49 (ddd)</td>
<td>27</td>
<td>19.8 (q)</td>
<td>0.85 (d)</td>
</tr>
<tr>
<td>4</td>
<td>38.9 (t)</td>
<td>2.21 (brt), 2.27(ddd)</td>
<td>28</td>
<td>23.0 (t)</td>
<td>1.23 (m), 1.28 (m)</td>
</tr>
<tr>
<td>5</td>
<td>140.4 (s)</td>
<td></td>
<td>29</td>
<td>12.0 (q)</td>
<td>0.86 (t)</td>
</tr>
<tr>
<td>6</td>
<td>122.1 (d)</td>
<td>5.37 (m)</td>
<td>&quot;Glucose moiety&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>31.9 (t)</td>
<td>1.46 (m), 1.53</td>
<td>1'</td>
<td>99.6 (d)</td>
<td>4.60 (d)</td>
</tr>
<tr>
<td>8</td>
<td>31.8 (d)</td>
<td>1.96 (m)</td>
<td>2'</td>
<td>71.5 (d)</td>
<td>4.97 (dd)</td>
</tr>
<tr>
<td>9</td>
<td>50.2 (d)</td>
<td>0.91 (m)</td>
<td>3'</td>
<td>72.9 (d)</td>
<td>5.22 (t)</td>
</tr>
<tr>
<td>10</td>
<td>36.7 (s)</td>
<td>4'</td>
<td>4'</td>
<td>68.7 (d)</td>
<td>5.06 (dt)</td>
</tr>
<tr>
<td>11</td>
<td>21.2 (s)</td>
<td>1.48 (m)</td>
<td>5'</td>
<td>71.7 (d)</td>
<td>3.69 (dd)</td>
</tr>
<tr>
<td>12</td>
<td>39.7 (t)</td>
<td>1.15 (m), 2.00 (m)</td>
<td>6'</td>
<td>62.0 (t)</td>
<td>4.24 (dd), 4.15 (dd)</td>
</tr>
<tr>
<td>13</td>
<td>42.3 (s)</td>
<td>2'-OAc</td>
<td>20.6, 169.4</td>
<td>2.03 (s)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>56.7 (d)</td>
<td>0.99 (m)</td>
<td>3'-OAc</td>
<td>20.6, 169.4</td>
<td>2.02 (s)</td>
</tr>
<tr>
<td>15</td>
<td>24.8 (t)</td>
<td>1.60 (m)</td>
<td>4'-OAc</td>
<td>20.7, 170.3</td>
<td>2.06 (s)</td>
</tr>
<tr>
<td>16</td>
<td>27.2 (t)</td>
<td>2.04 (m)</td>
<td>&quot;Acid moiety&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>56.1 (d)</td>
<td>1.10 (m)</td>
<td>1</td>
<td>173.5 (s)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>11.8 (q)</td>
<td>0.69 (s)</td>
<td>2</td>
<td>34.1 (t)</td>
<td>2.34 (t)</td>
</tr>
<tr>
<td>19</td>
<td>19.3 (q)</td>
<td>1.00 (s)</td>
<td>3</td>
<td>24.8 (t)</td>
<td>1.60 (m)</td>
</tr>
<tr>
<td>20</td>
<td>36.1 (d)</td>
<td>1.36 (m)</td>
<td>4</td>
<td>28.9 (t)</td>
<td>1.30 (m)</td>
</tr>
<tr>
<td>21</td>
<td>18.8 (q)</td>
<td>0.94 (d)</td>
<td>5'</td>
<td>29</td>
<td>1.26 (m)</td>
</tr>
<tr>
<td>22</td>
<td>33.9 (t)</td>
<td>1.01 (m), 1.33 (m)</td>
<td>CH$_3$</td>
<td>14.1 (q)</td>
<td>0.903 (t)</td>
</tr>
<tr>
<td>23</td>
<td>45.8 (d)</td>
<td>0.93 (m)</td>
<td>&quot;CH$_2$&quot; (double allylic C)</td>
<td>25.6 (t)</td>
<td>2.76 (t)</td>
</tr>
</tbody>
</table>
Comparison of the sugar protons of the non-acetylated natural compounds δ 4.38 d (J = 7.7), H-1'; 3.36 m, H-2'; 3.56 t (J = 8.7), H-3'; 3.38 m, H-4'; 3.45 m, H-5'; 4.50 dt (J = 12.1, 4.0) and 4.26 br d (J = 12.1, 2H-6') and the acylated one (Table 1) exhibited a downfield shift of H-2', 3' and 4' after the acetylation, while H-6' remained unchanged, indicating that the natural compound is acylated on the primary alcohol. The ester was evident from the 173.5 ppm resonance and its locality on the CH₂(6)OH group was clear from a HMBC correlation from 6'-protons to C1'' - the ester carbonyl group.

Comparison of various samples of 6-AGS exhibited identity of the β-sitosterol and the glucose molecules in all samples, and differences in the acylating fatty acid moieties. The molecular ion of the triacetate, m/z 964, suggested an unsaturated C₁₇H₃₁CO₂H acid as the glucose acylating molecule (964 = 414 (β-sitosterol) + 306 (glucose triacetate) + 280 (C₁₇H₃₁CO₂H) - 36 (2H₂O)). As mentioned above, the major unsaturated acid possesses a –CH=CH–CH₂–CH₂– unit.

The final structural determination of the fatty acid moiety was established by means of basic hydrolysis of 6-AGS followed by GC-MS analysis. The acyl moiety was found to consist primarily of palmitoyl and linoleyl (possessing the double allylic methylene unit) and minor amounts of stearoyl and oleyl.

For comparison and bioactivity purposes the synthesis of several 6-acyl derivatives was undertaken. The spectroscopic properties of the individual synthetic 6-acyl derivatives of β-sitosteryl-β-D-glucoside were identical to those of the isolated product. The two compounds showed the same Rf and retention time in chromatography (TLC and HPLC respectively). The synthesis of several 6-O-acyl-β-D-glucosyl-β-sitosterols followed a method published earlier [Kiribuchi, T., et al., Supra] with minor modifications.

**Anti-cancer activity**

Anti-cancer activity of the purified compounds was determined by solubilization the compounds in THF:Tween-80 mixture. The activity of 6-AGS was substantiated by experiments in which 6-AGS, purified from fig latex, was
added back to partially purified fig latex rendered non-active by removal of 6-AGS (Fig. 1). As shown in Fig. 2, the growth of Raji cells was inhibited by over 50% following their exposure to 6-AGS at concentrations of 25 to 50 μg/well. Similar results were obtained by addition of synthetically prepared derivatives. Of the compounds tested so far, the palmitoyl derivative (6-0-palmitoyl-β-D-glucosyl-β-sitosterol) (6-PGS) (Fig. 2) was the most effective. The stearyl and linoleoyl derivatives were somewhat less active.

The anti-cancer activity of 6-AGS was observed not only in tests with cells of the Raji line but also with other cell lines. The various cell lines were incubated for 3 days in the presence of two concentrations of 6-AGS. The inhibition of the growth of various cells by 6-AGS was calculated as a percentage of cells grown without addition of inhibitory compounds. As shown in the following Table 2, two concentrations of 6-AGS tested had a similar inhibitory effect on various leukemia and lymphoma cells grown in suspension and on epithelial cancer cells which were grown attached to the wells.

**Table 2 - Inhibition of the growth of cancer cells by exposure to 6-AGS**

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Origin of cell line</th>
<th>Inhibition of growth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>25 μg/ml</td>
</tr>
<tr>
<td>Raji</td>
<td>Burkitt B cell lymphoma</td>
<td>45.8</td>
</tr>
<tr>
<td>DG-75</td>
<td>Burkitt B cell lymphoma</td>
<td>40.6</td>
</tr>
<tr>
<td>Jurkat</td>
<td>T-cell leukemia</td>
<td>61.5</td>
</tr>
<tr>
<td>HD-MAR</td>
<td>T-cell leukemia</td>
<td>56.6</td>
</tr>
<tr>
<td>DU-145</td>
<td>Prostate cancer</td>
<td>61.3</td>
</tr>
<tr>
<td>MCF-7</td>
<td>Mammary cancer</td>
<td>56.6</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Previous work had shown that fig latex contains components that exert anti-cancer activity [Krispil et al., Ullman et al., Supra] but the nature of the active compounds was not determined.
A mixture of closely related compounds with anti-cancer activity was now isolated from fig latex. This mixture was shown to consist of several 6-AGS. A number of constituents, which were prepared synthetically showed similar activity on cancer cells. The palmitoyl derivative (6-O-palmitoyl-β-D-glucosyl-β-sitosterols) was the most effective. The stearyl and linoleoyl derivatives were also active.

The finding that the active agents isolated from fig latex are 6-O-acetyl-β-D-glucosyl-β-sitosterols is of considerable interest. Acylglucosylsterols are widely distributed in higher plants [Kiribuchi, T., et al., Osagie, A.U., et al., MacMurray, et al., Kinitia, P.K., et al., Kiribuchi, T., et al., Nippon Shinyaku Co. Ltd., Nordby, H.E., et al., Supra], some of which, such as soybeans and chickpeas, comprise an important food source, especially in East Asia. Similar compounds have been found to possess anti-mutagenic activity when orally administered to mice. 6-O-palmitoyl-β-D-glucosyl-β-stigmasta-5,25(27)-dien was found to be active at a dosage range of 12.5-50 µg/g [Guevara, A.M., et al., Mut. Res., 230:121-126, 1990]. Other reports have indicated that 6-O-palmitoyl-β-D-glucosyl-β-sitosterol is orally bioavailable [Nippon Shinyaku Co.Ltd., supra] and it has been shown that β-sitosteryl-β-glucoside is absorbed from the intestinal tract by lipoproteins in vivo [Seki, J., et al., J. Pharm. Sci., 74:1259-1264, 1985].

Acylglucosylsterols have also been isolated from snake and chicken epidermis. It was speculated that since the molecule contains two lipophytic arms (the fatty acid and the sterol moieties) stretching outward from a central hydrophilic glucosyl unit, it could function as a molecular rivet which can hold together adjacent lamellar structures and might form the water barrier mechanism of birds and snakes [Abraham, W., et al., J. Lipid Res., 28:446-449, 1987; and Wertz, P.W., et al., J. Lipid Res., 22, 427-435, 1996]. In a similar manner, such a molecular interaction may affect adverse changes in membrane permeability of malignant cells and thus may lead to their death. It will be important to further determine the in vivo activity of such compounds and their mode of action.
CLAIMS:

1. A compound of the following formula (I):

\[
\begin{align*}
\text{OC(O)R} & \quad \text{OC} & \quad \text{OH} \\
\text{HO} & \quad \text{O} & \quad \text{O} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

wherein R represents an acyl group, for use as an agent for inhibiting undesired cell proliferation.

2. The compound of Claim 1, wherein R is selected from (CH₂)₄CH₃, (CH₂)₁₆CH₃, (CH₂)₇CH=CH(CH₂)₇CH₃ and (CH₂)₇CH=CHCH₂CH=CH(CH₂)₄CH₃.

3. The compound of Claim 1, wherein R represents a palmitoyl group.

4. The compound of Claim 1 or 2, for use as an agent for the treatment or prevention of cancer.

5. The compound of any one of the preceding claims, being a naturally occurring compound or a synthetic product.

6. The compound of Claim 4, obtained from a fig latex extract.

7. The compound of any one of the preceding claims for use as a food additive.

8. The compound of any one of the preceding claims obtained by extraction from fig latex, said extraction comprises filtering fig latex under conditions which allow the separation of an aqueous filtrate from polymeric material present in said latex; collecting said aqueous filtrate, and treating said aqueous filtrate to isolate a compound of formula (I) or a mixture of compounds of formula (I).
9. A composition comprising a physiologically acceptable carrier and an amount of at least one compound of the general formula (I):

\[
\begin{align*}
\text{OC(O)R} & \\
\text{O} & \\
\text{OH} & \\
\text{O} & \\
\end{align*}
\]

wherein R represents an acyl group, the amount being such that when said composition is provided to an individual it is effective for achieving a therapeutic effect, the therapeutic effect comprises inhibition of undesired cell proliferation.

10. The composition of Claim 9, wherein R is selected from \((\text{CH}_2)_{14}\text{CH}_3\), \((\text{CH}_2)_{16}\text{CH}_3\), \((\text{CH}_2)_7\text{CH} = \text{CH} (\text{CH}_2)_7\text{CH}_3\) and \((\text{CH}_2)_7\text{CH} = \text{CHCH}_2\text{CH} = \text{CH} (\text{CH}_2)_4\text{CH}_3\).

11. The composition of Claim 10, wherein R represents a palmitoyl group.

12. The composition of any one of Claims 9-11, wherein said therapeutic effect comprises inhibition of tumor cell proliferation.

13. The composition of any one of Claims 9-12, wherein said compound of formula (I) is a naturally occurring compound or a synthetic product.

14. The composition of Claim 13, comprising a mixture of compounds of formula (I).

15. The composition of Claim 14, wherein said at least one compound of formula (I) is obtained from a fig latex extract.

16. The composition of Claim 15 wherein said at least one compound of formula (I) is obtained by filtering fig latex under conditions which allow the isolation of an aqueous filtrate from polymeric material present in said latex; collecting said aqueous filtrate, and treating said aqueous filtrate to isolate a compound of formula (I) or a mixture of compounds of formula (I).
17. The composition of Claim 16, wherein said treatment of aqueous filtrate comprises one or more extractions with one or more organic solvents.
18. The composition of any one of Claims 9-17, for use as a food additive.
19. Use of at least one compound of the following general formula (I):

\[
\text{[Chemical structure image]}
\]

wherein R represents an acyl group, for the preparation of a composition, the composition comprising an amount of said compound effective in achieving a therapeutic effect, the therapeutic effect comprising inhibition of undesired cell proliferation.
20. The use of Claim 16, wherein R is selected from \((\text{CH}_2)_4\text{CH}_3\), \((\text{CH}_2)_6\text{CH}_3\), \((\text{CH}_2)_7\text{CH} = \text{CH}(\text{CH}_2)_7\text{CH}_3\) and \((\text{CH}_2)_7\text{CH} = \text{CHCH}_2\text{CH} = \text{CH}(\text{CH}_2)_4\text{CH}_3\).
21. The use of Claim 20, wherein said R represents a palmitoyl group.
22. The use of any one of Claims 19-21, wherein said therapeutic effect comprises inhibition of tumor cell proliferation.
23. The use of any one of Claims 19-22, wherein said compound of formula (I) is a naturally occurring compound or a synthetic product.
24. The use of Claim 19, wherein said compound of formula (I) is derived from fig latex extract.
25. The use of Claim 19, wherein said composition is in a form suitable for use as a food additive.
26. A method for inhibiting undesired cell proliferation comprising contacting said cells with at least one compound of the following formula (I):
wherein R represents an acyl group.

27. The method of Claim 26, comprising contacting said cells with at least one compound of formula (I), wherein R is selected from (CH$_2$)$_{14}$CH$_3$, (CH$_2$)$_{16}$CH$_3$, (CH$_2$)$_{18}$CH=CH(CH$_2$)$_7$CH$_3$ and (CH$_2$)$_{18}$CH=CHCH$_2$CH=CH(CH$_2$)$_8$CH$_3$.

28. The method of Claim 27, wherein said R represents a palmitoyl group.

29. The method of any one of Claims 26-28, for inhibiting tumor cell proliferation.

30. The method of any one of Claims 26-29, wherein said compound of formula (I) is a naturally occurring compound or a synthetic product.

31. The method of Claim 26, wherein said compound of formula (I) is derived from fig latex extract.

32. A method for the treatment or prevention of a disease or disorder associated with undesired cell proliferation, the method comprising administering to a subject in need, a therapeutically or prophylactic effective amount of at least one compound of the following formula (I):
wherein R represents an acyl group.

33. The method of Claim 32, comprising administering to said individual at least one compound of formula (I), wherein R is selected from (CH₂)₁₄CH₃, (CH₂)₁₆CH₃, (CH₂)₇CH=CH(CH₂)₇CH₃ and (CH₂)₇CH=CHCH₂CH=CH(CH₂)₄CH₃.

34. The method of Claim 33, wherein said R represents a palmitoyl group.

35. The method of any one of Claims 32-34, for the treatment or prevention of cancer.

36. The method of any one of Claims 32-35, wherein said compound of formula (I) is a naturally occurring compound or a synthetic product.

37. The method of Claim 33, wherein said compound of formula (I) is derived from fig latex extract.