Medicinal Aspect of Saponins shows their wide range of Pharmacological/Biological activities

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Summary

Saponins (saponosides) belong to a group of secondary metabolites, widely distributed mainly, but not exclusively, among plants. The saponins are naturally occurring surface-active glycosides. They are reported to occur in over 500 species from over 90 families of both edible and nonedible plants. Chemically, saponins are glycosides consisting of a sugar moiety and non-sugar aglycone, called also sapogenin. Depending on the number of sugar chains attached to the aglycone, mono-, bi- and tridesmosides are distinguished. According to the structure of aglycone, saponins are classified into steroidal and triterpenoid.
Saponins have a high ability to bind to cell membrane sterols, which is responsible at least in part for their biological activities. They reveal also strong haemolytic properties, which differ depending on the saponin type and its aglycone structure. Saponins exhibit a wide range of biological properties and are believed to be one of the key biologically active constituents of plant drugs used in folk, especially Far East medicine. Saponins are also widely used in conventional medicine (i.e. expectorants, hypocholesterolemic drugs). Moreover many studies in vitro and in vivo exhibited their anti-inflammatory, antimutagenic, antiviral, antibacterial, antifungal, analgesic, and antitumour activities. The latter is the most promising because of its possible future therapeutical application, since many cancer cell lines are more vulnerable to saponins than normal cells. Its cytotoxicity in most cases is the result of apoptosis; nevertheless additional studies including determination of the inhibitory mechanisms of saponins should be addressed. There have been several reviews in recent years of published reports about various properties of saponins. Most of them, however, deal with either specific properties or specific sources of saponins. The purpose of the present review is to provide an overview of the extremely diverse biological activities of saponins, relate these to their structure and try to understand the molecular mechanism of their activity, as far as the available literature permits. It is hoped that the information collated here will provide the reader with information regarding the various potential applications of saponins, and stimulate further research into these compounds.

Introduction

Saponins occur constitutively in a great many plant species, in both wild plants and cultivated crops. In cultivated crops the triterpenoid saponins are generally predominant, while steroid saponins are common in plants used as herbs or for their health-promoting properties [1]. Triterpenoid saponins have been detected in many legumes such as soybeans, beans, peas, lucerne, etc. and also in alliums, tea, spinach, sugar beet, quinoa, liquorices, sunflower, horse chestnut, and ginseng. Steroid saponins are found in oats, capsicum peppers, aubergine, tomato seed, alliums, asparagus, yam, fenugreek, yucca and ginseng.

One example of an extensively studied group of triterpenoid saponins is produced from *Quillaja saponaria*, a tree native to the Andes region. *Yucca schidigera* is the most common commercial source of steroid saponins. Many of the most important saponins are present in the roots of ginseng (*Panax ginseng*), soybeans (*Glycine max*) and plants of Bupleurum genus.

They are mainly produced by plants, but also by lower marine animals and some bacteria [2]. Saponins are important compounds of plants and contain an aglycone with steroidal (C_{27}) or triterpene (C_{30}) structure bound to a mono- or oligosaccharide carbohydrate chain, composed of pentoses, hexoses or uronic acids. They derive their name from their ability to form stable, soap-like foams in aqueous solutions. This easily observable character has attracted human interest from ancient times. Saponins consist of a sugar moiety usually containing glucose, galactose, glucuronic acid, xylose, rhamnose or methylpentose, glycosidically linked to a hydrophobic aglycone (sapogenin) which may be triterpenoid in nature. Common for all types of saponins are their surface-active properties and the ability to form stable foam in water solutions. This property makes saponins applicable as components of household detergents and fire extinguishers. In general, very little is known about the enzymes and biochemical pathways involved in saponin biosynthesis.

Triterpenoid saponins are synthesized *via* the isoprenoid pathway by cyclisation of 2, 3-oxidosqualene to give primarily oleanane (β-amyrin) or dammarane triterpenoid skeletons. The genetic machinery required for the elaboration of this important family of plant secondary metabolites is as yet largely uncharacterized, despite the considerable commercial interest in this important group of natural products. This is likely to be due in part to the complexity of the molecules and the lack of commercially available pathway intermediates for biochemical studies.

Pharmacological activity

1. Hypocholesterolemic activity of saponins

Saponins remain within the gastrointestinal tract**.** Some interact directly with cholesterol producing an insoluble complex which prevents cholesterol absorption [3**].** Others appear to affect cholesterol metabolism indirectly by interacting with bile acids and increased faecal excretion of bile acids is observed in response to feeding saponins of this type (Oakenfull et al. 1979, 1984). Bile acids thus diverted from the enterohepatic cycle would be replaced by hepatic synthesis from cholesterol (Heaton, 1972). Oakenfull & Sidhu, 1983 measured rates of absorption of bile acids by perfused loops of small intestine in vivo (in the rat) and found that absorption from micellar solutions is greatly reduced compared with absorption from solutions containing no saponin. Thus, there may be a simple physico-chemical explanation for the effects of dietary saponins on cholesterol and bile acid metabolism.

2. Hepatoprotective Effect of Saponins

The effects of steroidal sapogenin extract from bitter yam or commercial diosgenin on liver enzyme changes were investigated by F. O. Omoruyi [5]. Diabetic male Wistar rats were fed diets supplemented with 1% steroidal sapogenin extract or commercial diosgenin for three weeks. Plasma glucose levels and the activities of hepatic glucose-6-phosphatase, pyruvate kinase and glucose-6-phosphate dehydrogenase were assessed. Liver total cholesterol, HDL-cholesterol and total phospholipid were also measured. The increase in liver glucose uptake is partly due to the alterations in the hepatic membrane cholesterol to phospholipid ratio with resultant partial restoration of glycolysis towards normal and subsequent decrease in gluconeogenesis. This also, contributes to the hypoglycemic property of sapogenin. There are conflicting reports in literature on the effect of saponin on the kidney.

3. Inhibition of Gastric Emptying and Central Nervous System

The speed of gastric emptying is important in the regulation of glucose homeostasis [5]. Gastric emptying abnormalities are common in diabetic patients and animals [6]. The usual situation in patients with diabetes is delayed gastric emptying. But it was reported that gastric emptying occurred faster in some type 2 diabetic patients [7], type 1 diabetic patients (Pehling et al., 1984; Nowak et al., 1990), and diabetic rodents (Nowak et al., 1994; Chang et al., 1996; Green et al., 1997) compared with healthy controls. Some studies have shown that obese subjects had accelerated gastric emptying compared with healthy controls [8]. Treatment with insulin and other hypoglycemic agents can increase gastric emptying in patients and animals with diabetes mellitus. More rapid gastric emptying rates in patients with diabetes mellitus would result in more rapid absorption of food, and therefore higher postprandial glucose levels. Consequently, slowing of gastric emptying will prolong the postprandial absorption of food, with a resultant improvement in blood glucose control. Therefore, the inhibition of the brain, but not by the i.v. injection of fructose, a sugar that cannot cross the blood-brain barrier to be used by the brain [9] and yet is used readily by peripheral tissues. The CNS participates in the inhibition of gastric emptying by momordin Ic a kind of saponins. The sympathetic nervous system can play an important role in gastric emptying. For example, the sympathetic activation may enhance prostaglandins synthesis to modulate gastric emptying (Kuratani et al., 1994; Stein et al., 1994). Therefore, the mechanism of the sympathetic nervous system needs to be considered in the inhibitions of gastric emptying by momordin Ic.

4. Role in Diabetes

Most of the research activities on bitter yam have focused on the role sapogenin play in the management of diabetes. Changes in weight, activities of carbohydrate digestive and transport enzymes, alterations in the intestinal morphology, changes in blood lipids, reduction in lipid peroxidation and the prevention of liver damage associated with diabetes have all been attributed to bitter yam sapogenin supplementation. Also, the possible exploitation of bitter yam for nutraceutical/pharmaceutical purposes is based on the high saponin content. Ruales and Nair [10], reported that saponins increased the activity of α-amylase significantly. They attributed the increase in α-amylase activity to detergent like properties of the saponins. The synergistic action of the phytosterol and sapogenin mixture may account for the higher α-amylase activity in the sapogenin extract compared to pure commercial diosgenin [11]. The report on amylase activity thus suggests that more products of carbohydrate digestion would be formed but it did not translate to increase fasting blood glucose. Bitter yam induces decrease in Na^+-K^+-ATPase activity with resultant impairment of glucose translocation into the blood from the gut and decrease in blood glucose [11]. The proposition is that the disruption of the mucosal morphology is sufficient to interfere with the absorption dynamics and the changes in amylase, disaccharidases and Na^+–K^+–ATPase activities and contribute to the decrease in blood glucose.

5. Role in Obesity

The bioactive principles responsible for anti-obesity property have been determined to be mainly due to spirosta-steroidal saponins, spirosta-steroidal alkaloids and galacto-glucan oligosaccharides. Most effective as an obesity control agent is the spirosta-steroidal saponins. Pharmaceutical, nutritional and veterinary use of this inventive composition is also disclosed. The hypolipidemic effect of diosgenin has been extensively studied. Jeon et al. [12], reported increased fecal quantity of rats fed on Chinese yam extract by more than 40% as compared with that of controls. Cayen and Dvornik [13] reported the effect of diosgenin on lipid metabolism in rats. In their study, rats were fed diosgenin for 1 week.

This resulted in the inhibition of cholesterol absorption and also a redistribution of serum lipoproteins decreased the concentration of low-density lipoproteins (LDL) while increasing that of high-density lipoproteins (HDL) in cholesterol fed rats. No effect was observed in normal rats. This increase in HDL-cholesterol level is advantageous in the treatment of hyperlipidemia as high HDL-cholesterol levels protect against cardiovascular disease. HDL-cholesterol delivers peripheral cholesterol to the liver for excretion from the body [14].

Sapogenin, on the other hand reduced liver cholesterol concentrations, but not phospholipids. Several mechanisms have been postulated for the action of saponins, but the most frequently cited mechanism is their physical interaction with luminal cholesterol resulting in the precipitation of a cholesterol complex. This inhibition of cholesterol is accompanied by a stoichiometric increase in the excretion of fecal neutral sterols [15]. Other proposed mechanisms for the inhibition of cholesterol absorption by saponins include: (a) formation of complexes with membrane cholesterol or the extraction of cholesterol from the membranes, (b) effect on the permeability of the intestine as well as (c) competition with cholesterol for micellar solubility.

High levels of total cholesterol, triglycerides and LDL-cholesterol are major coronary risk factors [16]. Wilson [17] reported a decrease in coronary risk with increased HDL cholesterol but most drugs used in the management of hypercholesterolemia decrease both total cholesterol and HDL-cholesterol. Sapogenin does not significantly reduce hepatic total cholesterol and triglyceride levels. Therefore, a decrease in plasma HDL cholesterol by sapogenin extract [18] translate to decrease in the amount of cholesterol that reaches the liver resulting in the increase in the rate of hepatic cholesterol synthesis through the depression of HMG COA reductase by diosgenin [13]. It is well known that HDL plays an important role in the transport of cholesterol from peripheral cells to the liver by a pathway called “reverse cholesterol transport”. Therefore, a decrease in plasma and liver VLDL-LDL-cholesterol and the increase in liver HDL cholesterol level confer some beneficial effects in the use of bitter yam sapogenin in the management of hypercholesterolemia in diabetes [17].

6. Anti-tumor Activity of the Ginsenoside

Cancer cells are typically distinguished from normal cells by their resistance to apoptosis and the maintenance of telomere integrity through telomerase reactivation. Thus, telomerase is an outstanding cancer marker and a key target for anti-tumor therapy. Caspase-8 activation has been investigated in association with tumor necrosis factor-receptor (TNF-R) family-mediated apoptosis. Steroidal sapogenin has been shown to have potential for cancer chemo prevention, especially as apoptosis inductors [19]. Apoptosis is a major process responsible for cell death in various physiological events. Leger et al. [20] showed that diosgenin induced apoptosis in human erythroleukemia (HEL) cells. The apoptotic signaling pathway of diosgenin is associated with a decrease in NF-kB activation and stimulation of p38 MAPK in erythroleukemia K562 cells [21]. The induction of apoptosis by diosgenin is independent of cyclo-oxygenase-2 (COX-2) expression in K562 cells and this is in contrast to HEL cells where diosgenin induced apoptosis correlate with COX-2 up-regulation [22]. The effects of sapogenin extract at the molecular levels are not known. For a detailed understanding of the mechanisms of action of sapogenin extract, the toxicology, responses at the molecular level, HMG CoA reductase activity and anti-oxidative enzymes need further investigation.

7. Hemolytic Activity, Degradation and Absorption Mechanism of Sapogenin

Saponins display a tremendous structural diversity and a wide spectrum of biological activities which includes hemolytic activity that is shared by many structurally disparate saponins [22]. Saponins hemolyze red blood cells by nonspecific interactions with membrane proteins, phospholipids and cholesterol of erythrocytes with the resultant increase of permeability and loss of hemoglobin. The hemolytic property of saponins constitutes a major

drawback in the therapeutic potentials of saponins. However, there are saponins with low or no hemolytic effect [23]. Tawab et al. [24], identified the degradation products of ginsenosides, a saponin in plasma and urine of humans and attributed them to the action of gut microorganisms, intestinal enzymes or gastric fluid. They reported that only the monoglucosylated degradation products of the protopanaxatriol ginsenosides are absorbed due to greater water solubility and not the corresponding aglycones. Ingested saponins are also rapidly hydrolysed in the rumen of lambs into free sapogenins [24]. Sapogenins are then partly oxidized and reduced at C_3 to form episapogenins. Both episapogenins and sapogenins are absorbed in the jejunum and duodenum and transported to the liver where epimerization and conjugation with glucuronic acid and excretion into the bile occur. However, the hemolytic activity and degradation products of sapogenin extract from bitter yam need to be investigated especially as it relates to the composition of the extract (80% diosgenin and the other 20% made up of β-sitosterol, pennogenin, stigmasterol and Δ^3 diosgenin).

Conclusion

In conclusion, the changes in the activities of carbohydrate digestive and transport enzymes coupled with the alterations in the intestinal morphology by bitter yam sapogenin constitutes the mechanisms of action in the control of hyperglycemia in diabetes. The binding of intestinal lipids by bitter yam sapogenin extract is sufficient to cause a shift in the intestinal membrane permeability with the resultant decrease in the intestinal absorption of carbohydrates and lipids. Also, the alterations in intestinal morphology contribute to the changes in the lipid levels. The reduction in lipid peroxidation and the prevention of liver damage associated with diabetes are all beneficial in the management of diabetes mellitus. However, bitter yam sapogenin extract has an adverse effect on the body weight and the integrity of kidney membrane, which may limit its usage in the management of the disease. Also, future studies on the hemolytic effect and the degradation products of bitter yam sapogenin extract may further elucidate the molecular mechanism of action in diabetes.

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