The Pharmaceutical and Chemical Journal, 2019, 6(2):112-122

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

A Study on the Pharmacological Effects and Mechanism of Action of Alkaloids, Glycosides and Saponins

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Abstract Bioactive alkaloids, glycosides and saponins are phytoconstituents and belong to the secondary metabolites of plants kingdom. These constituents possesses many pharmacological properties such as antioxidant activity, antimicrobial effect, modulation of detoxification of enzymes and hormone metabolism, stimulation of the immune system, decrease of platelet aggregation procedure, possess antidiabetic, antihypertensive, antidepressants, analgesics and anticancer etc. properties. Now a days these compounds have received great attention worldwide as the sources of novel agents, important pharmaceutical intermediates and significant starting materials for a lot of synthetics or semi synthetics drugs due to potent pharmacological activities, higher safety profile, low toxicity and cost effectiveness. So the current study is designed to focus on the accumulation of sufficient information's about the above mentioned phytoconstituents regarding their pharmacological effects and mechanisms of action along with other significant properties.

Keywords Pharmacological effects, Mechanism of actions,Alkaloids, Glycoside, Saponins etc.

Introduction

Phytoconstituents such as alkaloids, glycosides and saponins are bioactive, naturally occurring chemical compounds found in plants, which provide broad spectrum health benefits for human beings [1]. They protect plants from different kinds of diseases and damage and contribute to the plant's color, aroma and flavor. Generally, the plant constituents that protect plant cells from environmental hazards including pollution, stress, drought, UV exposure and pathogenic attack are called as phytoconstituents [2,3]. Currently, it is noticeably recognized that they have roles in the protection of human health, when their dietary intake is significant. More than 4,000 phytoconstituents have been cataloged [4] and are classified by defensive function, bodily features and chemical characteristics [5] and about 150 phytoconstituents have been studied in detail [4]. In wide-ranging dietary phytoconstituents are found in fruits, vegetables, legumes, whole grains, nuts, seeds, fungi, herbs and spices [3].These phytoconstituents are accumulated in different parts of the plants including the roots, stems, leaves, flowers, fruits or seeds [6]. Many of them, particularly the pigment molecules, are often concentrated in the outer layers of the various plant tissues. These compounds are secondary plant metabolites and have lot of biological properties such as antioxidant activity,

antimicrobial effect, modulation of detoxification enzymes, stimulation of the immune system, decrease of platelet aggregation and modulation of hormone metabolism and anticancer property. It is well-known that plants produce these chemicals to protect themselves, but recent investigates establish that many phytoconstituents can also protect human against a lot of diseases and health hazards [7]. Several studies have been done in evaluation of alkaloids, glycosides and saponins from various points of view for their wide range of pharmaceutical and medicinal activities. All these studies suggested and revealed the possible role for the same in the prevention and treatment of diseases. But still there is a scarcity of systematic or at a glance arrangement of these properties of bioactive major alkaloids, glycosides and saponins [8]. So the purpose of the present review is to provide an at a glance impression of the pharmacological effects and the molecular or receptor level mechanisms of action along with structures and sources of major alkaloids, glycosides and saponins components.

Alkaloid

Alkaloids are a class of naturally occurring organic compounds that mostly contain basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties [9].The nitrogen may exist as primary (1° amines), secondary (2° amines) or tertiary (3° amines) amine.

Physical Properties

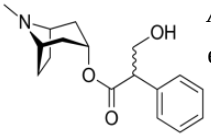
With few exemptions, all the alkaloids are colorless, crystalline solids with a sharp melting points or de-composition range. Some alkaloids are amorphous gum, while other coniine, spartine, nicotine etc. are liquid and volatile in nature. Some alkaloids are coloured in nature, eg. Betanidin is red, berberine is yellow and salts are copper-red in color. In general, the free bases of alkaloids are soluble in organic non-polar, immiscible solvents. The salts of some special alkaloids are soluble in water. In contrast, free bases are insoluble in water and their salts are also sparingly soluble in organic solvents. The alkaloids containing quaternary bases are only water soluble. Some of the pseudoalkaloids and protoalkaloids show higher solubility in water [10].

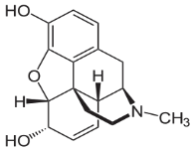
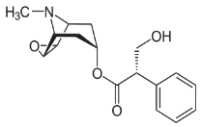
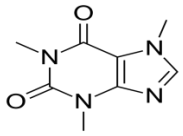
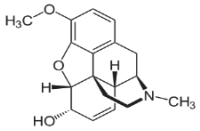
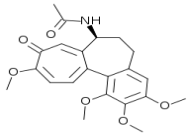
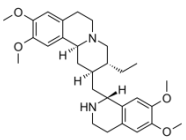
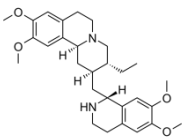
Chemical Properties

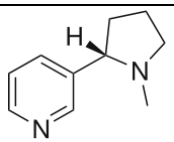
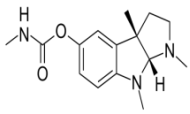
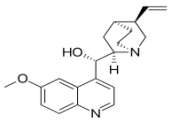
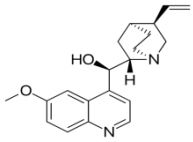
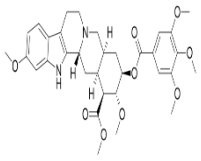
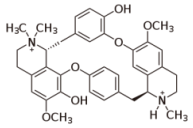
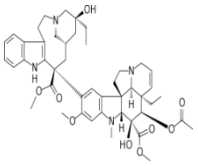
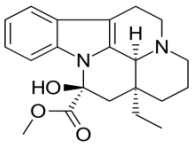
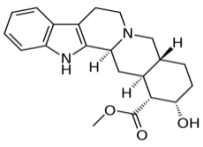
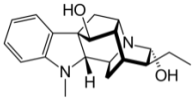
Most of the alkaloids are basic in reaction, due to availability of lone pair of electron on the nitrogen ring. The basic character of the alkaloid compound is enhanced if the adjust function groups are electron releasing. The alkaloid turns to be natural or acidic when the adjust functional groups are electron withdrawing like amide group which reduces availability of lone pair of electrons. But alkaloids exhibits basic characters are very much sensitive to decomposition and cause a problem during their storage.

Their salt formation with inorganic acid makes them stable and prevents their decomposition. The alkaloids may contain one or more number of nitrogen and it may exist in the form as primary ($R\text{-}NH_2$), eg. Mescaline, secondary amine (R2-NH), eg. Ephedrine; tertiary amine (R3-N), e.g. Atropine; and quaternary amine (R4N+X) eg. Tubocuarine chloride etc. In the last type, their properties vary from other alkaloids, owing to quaternary nature of nitrogen. Unsurprisingly, the alkaloids exist either in free form, as amine or as salt with acid or alkaloids N-oxides [11]. The alkaloids exhibit diversity of structure and also show an extraordinary spectrum of pharmacological activities and mechanisms of action which are tabulated bellow.

Table 1: Structures, Sources, Pharmacological effects and mechanism of action of different alkaloid compounds

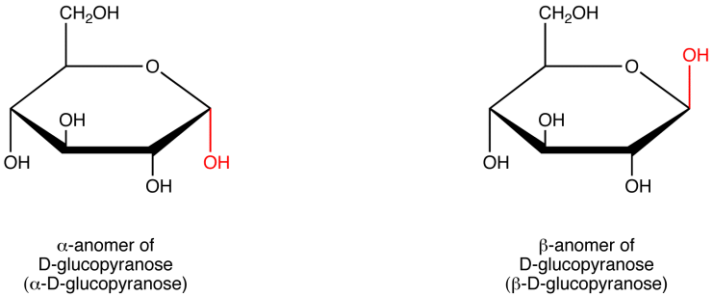
Compounds name	Structure	Source	Pharmacological action	Mechanism of action (M/A)
Atropine		*Atropa belladonna* extract	Anticholinergic. Suppress visually induced myopia both in animals and humans. Atropine increases the	Atropine counters the "rest and digest" activity of glands regulated by the parasympathetic nervous system, competitive antagonism to acetylcholine at

Compounds name	Structure	Source	Pharmacological action	Mechanism of action (M/A)
			release of the neurotransmitter dopamine produced hypothermia Increase heart rate and decrease secretion.	the muscarine-sensitive cholinoceptors. Atropine is a competitive antagonist of the muscarinic acetylcholine receptor types M1, M2, M3, M4 and M5 [12].
Morphine		Poppy straw of the *Opium Poppy* [13].	Analgesic	Morphine binds to μ, δ, κ opioid receptors and molecular signaling activates the receptors to mediate certain actions.
Hyoscyamine		From henbane, mandrake, jimson weed, tomato and deadly nightshade extract	Anticholinergic	Binding at muscarinic receptors in the salivary, bronchial, and sweat glands & in the eye, heart, and gastrointestinal tract.
Caffeine		Cocoa beans, kola nuts, tea leaves and coffee beans.	CNS stimulator, adenosine receptor antagonist	Caffeine increases energy metabolism throughout the brain but decreases at the same time cerebral blood flow, inducing a relative brain hypo perfusion.
Codeine		The dried milky exudate of the unripe seed capsule of the poppy.	Antitussive, analgesic	Codeine is an opioid and an agonist of the μ opioid receptor. It acts on the central nervous system to have an analgesic effect[14].
Colchicine		extracted from plants of the genus, autumncrocus.	Remedy for gout	Colchicine decreases leukocyte chemotaxis and phagocytosis and inhibits the formation and release of a chemotactic glycoprotein
Emetine		Roots of *U ragoga* Ipecac root.	antiprotoz oalagent, Emesis	Emetine inhibits protein synthesis in eukaryotic cells
Ergoline		Found in ergot fungi	Vasoconstriction, hallucinogenic, Uterotonic	5-HT1B/1D receptors likely mediate their acute antimigraine effects

Compounds name	**Structure**	**Source**	**Pharmacological action**	**Mechanism of action (M/A)**
Nicotine		Leaves of Nicotiana rustica & tobacco plant	stimulant, nicotinic acetylcholine receptor agonist.	Nicotine binds to nicotinic acetylcholine receptors on dopaminergic neuron
Physostigmine		Calabar bean and the Manchineel tree.	Inhibitor of acetylcholinester-ase	Physostigmine inhibits acetylcholinesterase & indirectly stimulates both nicotinic and muscarinic receptors
Quinidine		Bark of the cinchona tree	Antiarrhythmic	Getting incorporated in DNA strand, Inhibiting replication
Quinine		Cardinal's Bark	**A**ntipyretic, antimalarial	Getting incorporated in DNA strand, Inhibiting replication
Reserpine		Rauwolfia Vomitoria Root Bark.	Antihypertensive, sedative and hypnotic	Stimulate the central nervous system
Tubocurarine		Bark and stem of Chondodendron tomentosum	Muscle relaxant	Inhibiting the action of acetylcholine and blocking the neural transmission
Vinblastine, Vincristine		From the plant Vinca rosea Linn	Antitumor, Anticancer	Vinblastine binds to tubulin &inhibits microtubule formation, resulting in disruption of mitotic spindle.
Vincamine		From leaves of Vinca minor	Vasodilating, Antihypertensive	Increasing blood flow and oxygen supply to the brain.
Yohimbine		From the bark of the Pausinystalia yohimbe tree	Stimulant, Aphrodisiac	Yohimbe dilates the blood vessels and can lower blood pressure.
Ajmaline		Root of Rauwolfia serpentina	Antiarrhythmic	Acts by changing the shape and threshold of cardiac action potentials.

Glycoside

Glycosides are compounds that yield one or more sugars upon hydrolysis. The termglycoside is a generic term for natural product that is chemically bound to a sugar. Thus the glycoside composes of two parts: the sugar and the aglycone. The aglycon may be a terpene , a flavonoid, a coumarine or any other natural product. Glycoside showed extra chemical diversity. Among the sugars found in natural glycosides, D-glucose is the most abundant one, L rhamnose and L-fructose also occur quite ferequently. Of the pentoses: L-arabinose is more common than D-xylose. The sugar part can be disaccharide. Because of the cyclic structure of the sugar, two diastereoisomers of the glycoside exist depending on the configuration of the anomeric carbon. These diastereoisomers are called anomers and are designated as α and β. This classification depends on the glycosidic linkage (above the linkage is β), below the linkage is α. The first glycoside ever identified was amygdalin, by the French chemists Pierre Robiquet and Antoine Boutron-Charlard, in 1830 [15].



(Source: http://www.ochempal.org/index.php/alphabetical/a-b/alpha-anomer/)

Chemically, glycosides are usually mixed acetals in which the hydroxyl group on the anomeric carbon is replaced by a moiety possessing a nucleophilic atom. Thus the sugar moiety of a glycoside can be joined to the aglyconevia Oxygen atom (O-glycosides -1), Carbon atom (C-glycosides -2), Nitrogen atom (N-glycosides- 3) and Sulfur atom (S-glycosides-4).

Physical Properties:

- May be crystalline or amorphous.
- Soluble in water & dilute alcohol; Exception: Resin glycosides.
- Insoluble in organic solvents like $CHCl_3$Or ether.
- Aglycon soluble in non-polar solvents like benzene or ether.
- The presence or absence of various polarity contributing functional groups in the structure of the algycon portion would contribute to the degree of solubility in a given solvent e.g. thioglycosides are soluble in water partly because of the ionic sulfate residue.
- Easily hydrolyzed by mineral acid, eater & enzymes.
- Show optical activity, normally with levorotatory effects.
- Glycosides do not reduce Fehling`s solution until they are hydrolyzed.
- Believed to participate in growth regulation.

Chemical Properties:

Stability & hydrolytic cleavage:

- Glycosides can be hydrolyzed by heating with a dilute acid, where the glycosidic linkages are cleaved.
- Glycosidic linkages involving different kinds of sugars are hydrolyzed with different degrees by acid hydrolysis.

Based on the chemical properties, glycosides can be classified into Cardiac glycosides, Cyanogenic glycosides, Phenolic glycosides (flavonoids, lignans and other phenolic compounds), Aldehyde glycosides, Anthraquinone and Saponin glycosides (triterpenoid, sterol etc.). The pharmacological effects and mechanisms of action and few other

particulars e.g., compound's name, structures, sources etc. of different types of glycosides are arranged in the following table under the heading of cardiac and other glycosides.

Table 2: Structures, Sources, Pharmacological effects and mechanism of action of different kinds of cardiac glycosides

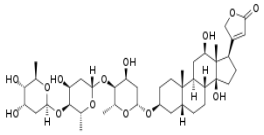
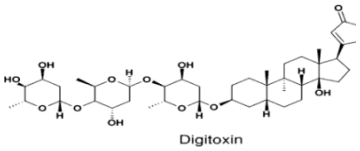
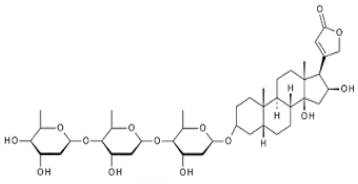
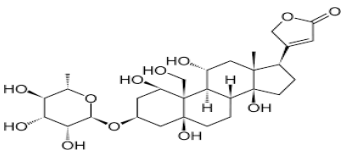
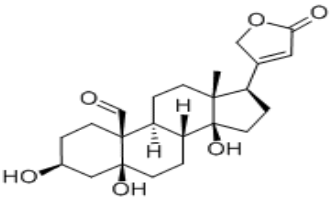
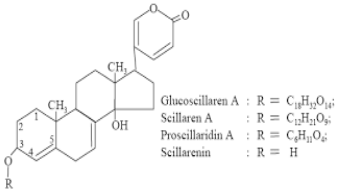
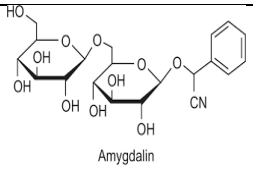
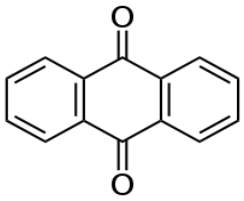
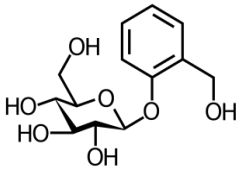
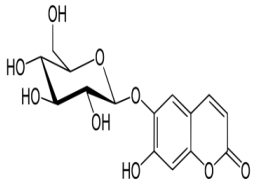
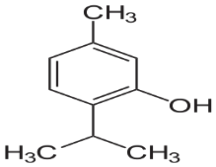
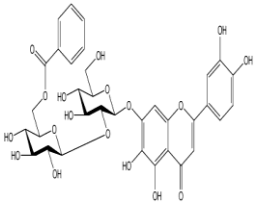
Group	Compo-und Names	Structure	Source	Pharmacological effects	Mechanism of Action
1. Digitalis glycosides	1. Digoxin		*Digitalis purpurea* (leaf)	In the heart digitalis (digoxin) has a direct effect on the myocardial contractility.	Digoxin inhibits the Na-K ATPase membrane pump.
	2. Digitoxin	 Digitoxin	*Digitalis lanata*(leaf)	In the heart digitalis (digitoxin) has a direct effect on electrophysiologic al function.	Digitalis compounds are potent inhibitors of cellular Na^+/K^+-ATPase
	3. Gitoxin		*Digitalis lanata*(leaf).	In the heart digitalis(gitoxin) has a direct effect on the myocardial contractility.	Digoxin inhibits the Na-K-ATPase membrane pump.
2. Strophan thus gratus glycoside	Ouabain		*Strophanthus gratus* (seed)	Ouabain is used to treat congestive heart failure and supraventricular arrhythmias.	Ouabain acts by inhibiting the Na+/K+-ATPase sodium-potassium ion pump (but it is not selective).
3. Strophan thus Kombe glycoside	K-strophan thin		Ripe seeds of *Strophanthus kombé*	The strophanthin K increases force of contractions of cardiac muscle.	k-strophanthidin is a cardiac glycoside which works as an inhibitorof Na^+ $/K^+$-ATPase
4. Bufadien olide	Squill bulb glycoside	 Glucoscillaren A : R = $C_{18}H_{32}O_{14}$; Scillaren A : R = $C_{12}H_{22}O_9$; Proscillaridin A : R = $C_6H_{12}O_6$; Scillarenin : R = H	*Urgineamaritima* (L.) Baker (Scillamaritima L.)	Squill extracts cause peripheral vasodilation and bradycardia in anesthetized rabbits.	Squill seems to have cardiac effects including positive inotropic and negative chronotropic effects

Table 3: Structures, Sources, Pharmacological effects and mechanism of action of different kinds other glycosides than cardiac glycosides

Groups	Compound Names	Structure	Source	Pharmacological effect	Mechanism of Action
1. Cyanogenic glycosides	Linamarin, Amygdalin	 Amygdalin	Bitter almonds (Amygdalin) Cassava root. Other sorghum, lima beans, stone fruits and bamboo shoots.	Amygdalin has been used for treatment of cancer.	Amygdalin has been shown to inhibit the adhesion of breast cancer cells, lung cancer cells.
2. Anthraquinone glycosides	sennoside A, B, C and D.		Ericaceae, Leguminosee	Anthraquinone have a laxative and Stimulatory effects.	Anthraquinone increase the motility so produce laxation.
3. Alcoholic glycosides	Salicin		Genus *Salix*	analgesic, antipyretic and anti inflammatory effects[16]	Modulator for the neurotransmitter GABA (gamma aminobutyric acid)
4. Coumarin glycosides	Apterin		Leaves of Psoraleacoryl ifolia.	Dilate coronary arteries and increase antithrombin level.	Act as Calcium channels blocker.
5. Phenolic glycosides	Arbutin		Found in the Common Bearberry Arctostaphylo suva- ursi.	Depigmenting action in human melanocyte cultures and antiseptic effect.	Competitive inhibition of tyrosine activity.
6. Flavonoid glycosides	Hesperidin, Naringin, Rutin		Lemon, sweet orange, Grapefruit and orange etc.	Antioxidant activity and Decrease capillary fragility.	Inhibit coagulation, thrombus formation or platelet aggregation

Saponins

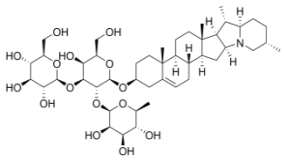
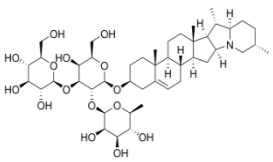
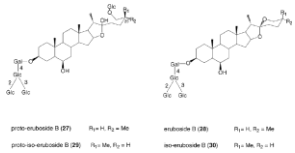
Saponins are a class of chemical compounds found in particular abundance in various plant species. More specifically, they are amphipathic glycosides grouped phenomenologically by the soap-like foam they produce when shaken in aqueous solutions, and structurally by having one or more hydrophilic glycoside moieties combined with a lipophilic triterpene or steroid derivative [17,18].Saponins, secondary metabolites with high molecular weight, are present in a wide range of plant species. They are distributed throughout the bark, leaves, stems, roots and even flowers of the plant kingdoms. They are bitter in taste and in recent years, have received considerable attention because of their various biological activities including hepatoprotective, anti-ulcer, anti-tumor, antimicrobial, adjuvant and anti-inflammatory activities. These compounds are composed of a lipid soluble aglycone consisting of either a sterol or more commonly a triterpenoid and water soluble sugar residues. Due to their amphiphilic nature, they are highly surface active and their biological activities are related to their chemical structures. Both ste-roidal and triterpenoids saponins show detergent properties. Saponins are also used for their effects on ammonia emissions in animal feeding [19].

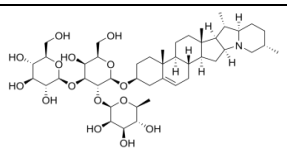
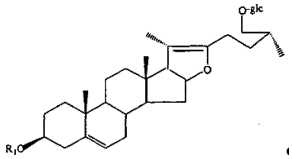
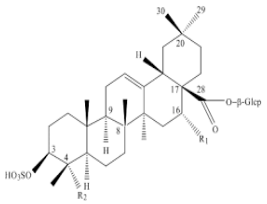
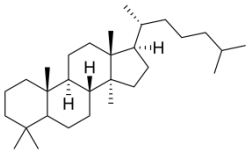
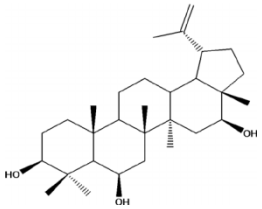
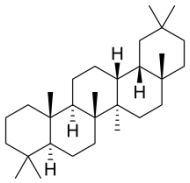
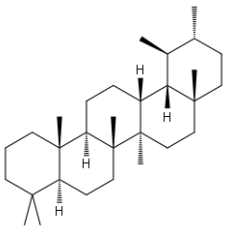
Properties of saponins

Saponins are generally soluble in water, soluble in hot water, dilute alcohol, insoluble in ether, benzene, chloroform and other lipophilic organic solvents, solubility better in aqueous butanol or pen-tanol, and can both layered with water, thusbutanol or pentanol can be used to extract saponin from the aqueous solution. Saponins hydrolysis generate secondary saponins, its solubility in water is low, but soluble in moderate polar acetone, alcohol, ethyl acetate, etc. If the saponin hydrolyzed totally and became sapogenins then its water solubility may even worse, and soluble in ether, benzene, chloroform and other low-polar solvents.

Like alkaloids and glycosides the pharmacological effects and mechanisms of action with some other particulars including compounds names, structures, sources etc. of different categories of saponins are arranged in the following table.

Table 4: Structures, Sources, Pharmacological effects and mechanism of action of different saponins

Compound Names	Structure	Source	Pharmacological effect	Mechanism of Action
Steroidal Saponins		Cyclopentanoper hydro derivatives	Surface tension reducing agent.	Produce pore in the membrane and increase the permeability.
Spirostanols Saponins		Monocotyledon angiosperm	Serum cholesterol levels lowering activity	By eliminating trans fats
Isospirostanol saponins		spirostanol skeleton	Ovulation induction activity	Stimulation of luteinizing hormone release

Pseudo-Spirostanols			five tetrahydrofuran rings	immune modulatory potential via cytokine interplay	By lowering anti immune modulatory potential
Furostanols			*Solanummacaonense*	Antineutrophilic inflammatory activity and cytotoxic effects on malignant tumor cells	Superoxide anion generation and elastase release were significantly inhibited
Triterpenoidalsaponin (Squalin)			*Pisumsativum*	Anti microbial and anti insect activity and adjuvant properties for vaccines	a specific inhibitor of diguanylatecyclase, a key regulatory enzyme in the synthesis of cellulose
Tetracyclic Triterpenes (Lanostane, Dammarane)			*Gynostemma pentaphyllum*	Enhance brain cognition function	By regulating brain neurotransmitter levels and inhibiting SLSE-induced neuronal injury
Pentacyclic Triterpenoid	1. Lupane		Vegetables, fruits and plant species	Cytostatic and cytotoxic effects anti-inflammatory, anti-HIV activities.	Induce apoptosis
	2. Oleanane		*Olea europaea*	Active against breast cancer	Induce apoptosis
	3. Ursane		Triterpenesapogenin	Active against chronic and acute inflammation	Inhibition of DNA topoisomerase and polymerase

Conclusion

Alkaloids are important class of secondary metabolites have been found to exhibit many important pharmacological properties such as muscle relaxation, analgesic, antitussive, antiprotozoal, antimalarial, antihypertensive, sedative, hypnotic, antitumour, aphrodisiac and antioxidant properties. Some examples of such significant alkaloids include atropine, morphine, hyoscyamine, caffeine, codeine, colchicine, emetine, ergoline, nicotine, physostigmine, quinidine, quinine, reserpine, tubocurarine, vinblastine, vincristine, vincamine, yohimbine, ajmaline etc. These are used for the curative purposes and are helpful for the mankind. With the advancements in the field of science and technology, alkaloids are being exploited for various purposes. Mechanism of actions of alkaloids are competitive antagonist of muscarinic receptor, stimulate μ, δ, κopoid receptors, increase of energy metabolism and decrease cerebral blood flow, inhibition of neurotransmitter release, decrease leukocyte chemotaxis, inhibit protein synthesis, stimulate nicotinic acetylcholine receptor, incorporating in DNA, inhibit microtubules, increase oxygen supply to tissues and changing cardiac action potential etc. We would like to conclude that alkaloids are useful for plants, humans, as well as animals. They can be employed for pharmaceutical purposes, due to its presence in almost all the vegetables and medicinal plants. Attention is required in testing this compound for the curative poses of the human diseases. Pharmacologically significant prominent one glycoside group is cardiac glycosides .This group includes digoxin, digitoxin, gitoxin, ouabain, K strophanthin significant compounds etc. Other glycosides group include cyanogeniceglinamarin, amygdaline, Alcoholic e.g. salicin, coamarin, apterin, Phenolic e.g. arbutin, Flavonoid e.g.hespiridine, naringin etc. The pharmacological effects of above mentioned glycoside are broad spectrum and include positive ionotropic effects, negative chronotropic effects, peripheral vasodilatory effects, bradycardia, anticancer and antiseptic, laxative, analgesic, antipyretic anti in-flammatory , antithrombin potentiation, depigmenting, antioxidant etc. effects. The prominent molecular mechanisms of different glycoside includes potential inhibition of Na^+ K^+ ATPase membrane pump, inhibitors of cellular adhesion, modulation of neurotransmitters, blocking of Ca^{++} channel and inhibition of tyrosine effects. Saponins are a diverse family of secondary metabolites. The member of this family are steroidal Saponins, Spirostanols Saponins, Isospirostanol saponins, Pseudo-Spirostanols, FurostanolsTriterpenoidal saponin (Squalin), Tetracyclic Triterpenes, (Lanostane, Dammarane), Lupane, OleananeUrsane etc.

The effects of saponin compounds include antimicrobial, anti-cholesterol, ovulation induction activity, potential immune modulation activity, chronic and acute anti-inflammatory effects, cytotoxic effects, cognition function enhancing activity, anticancer activity etc. They cause these activities in different mechanisms such as by increasing membrane permeability with producing pores, eliminating fat, stimulating luteinizing hormone release, lowering antiimmune modulation potential, generating superoxide anion and eliminating of elastage release , inhibiting diguanylateproduction, regulating brain neurotransmitter release, inducing apoptosis and inhibiting of DNA topoisomerase. It is believed that the natural role of these compounds is to protect against attack by potential pathogens, which would account for their antimicrobial activity. Although saponins are extremely toxic to cold-blooded animals, their oral toxicity to mammals is low. Due to their toxicity to various organisms, saponins can be utilized for their insecticidal, antibiotic, fungicidal and other pharmacological properties. The wide pharmacological diversity of alkaloids, glycoside and saponins regarding effects and mechanism of action has resulted in renewed interest. This research provides a summary of alkaloids, glycoside and saponins research especially on biological effects with their mechanisms of action.

Acknowledgments

This work was supported by Northern University Bangladesh, Dhaka, Bangladesh.

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