



Revive Herbal Capsule: A Review on the Mechanism of Action, Constituent Herbs and Phytochemicals

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Authors' contributions

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Review Article

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ABSTRACT

Revive capsule, also called Kedi Revive capsule is a polyherbal formulation manufactured by Kedi healthcare company limited in Hong Kong, China. The drug is widely used around the globe, especially in Africa and Asia for the treatment of erectile dysfunction or enhancement of libido in men. Each capsule contains 400 mg of the constituent herbs including 80 mg of herb Epimedii, 80mg of *Radix ginseng*, 40 mg of *Cordyceps militaris*, 80mg of *Tribulus terrestris*, 80mg of *Radix polygoni multiflori*, and 40 mg of *Eucommia ulmoides*, with its effects exerted four hours after administration via the oral route. The adult man dosage is two capsules (800 mg) to be taken once daily for at least 28 days (before significant improvements may be observed when used to treat erectile dysfunction). Phytochemical analysis of the drug reported the presence of flavonoids, cardiac glycosides, tannins, polyphenols, alkaloids and quinones. Due to its speculated use in the treatment of erectile dysfunction or enhancement of libido, it may be referred to as an herbal

phosphodiesterase type-5 inhibitor, that acts by selectively inhibiting the enzyme phosphodiesterase type-5, and thus enhancing increased arterial blood flow into the penis, which results in penile erection; however, the mechanism of action of this drug may be attributed to the contained phytochemicals. Additionally, due to its increased use, it is highly recommended that further studies be conducted on this drug to ascertain its effects on some biochemical components and vital organs of the body.

Keywords: Revive capsule; phosphodiesterase type-5 inhibitor; polyherbal; phytochemicals.

1. INTRODUCTION

Revive capsule (which is also referred to as Kedi Revive) is a formulation made from several herbs by Kedi healthcare company limited in Hong Kong, China. These various herbs used in the formulation of this capsule possess aphrodisiac properties [1]. The drug is said to be commonly used to treat erectile dysfunction or enhance libido in men, with its effects exerted four hours post-administration via the oral route; each capsule containing 400 mg of the constituent herbs comprising of 80 mg of herb Epimedii, 80 mg of *Radix ginseng*, 40 mg of *Cordyceps militaris*, 80 mg of *Tribulus terrestris*, 80 mg of *Radix polygoni multiflori*, and 40 mg of *Eucommia ulmoides* [1].

Ibama et al. [1] conducted a phytochemical screening on Revive capsule, and reported that the drug contains flavonoids, cardiac glycosides, tannins, polyphenols, alkaloids and quinones at a concentration of $20.48 \pm 1.18 \mu\text{g}/\text{mg}$, $2.76 \pm 0.15 \mu\text{g}/\text{mg}$, $1.43 \pm 0.43 \mu\text{g}/\text{mg}$, $25.4 \pm 0.19 \mu\text{g}/\text{mg}$, $23.87 \pm 0.44 \mu\text{g}/\text{mg}$, and $0.76 \pm 0.01 \mu\text{g}/\text{mg}$

respectively. The adult man dosage is two capsules (800 mg) to be taken once daily for at least 28 days (before significant improvements may be observed when used to treat erectile dysfunction). As a drug speculated to enhance penile erection, its mechanism of action of may be similar to that of sildenafil citrate, vardenafil and tadalafil, and may therefore be referred to as a phosphodiesterase type-5 inhibitor, exerting its pharmacological effects by selectively inhibiting an enzyme called phosphodiesterase type-5 (PDE-5) [1].

2. MECHANISM OF PENILE ERECTION/MECHANISM OF ACTION OF PDE-5 INHIBITORS

Phosphodiesterase type-5 inhibitors exert their pharmacological effects by selectively inhibiting an enzyme called phosphodiesterase type-5 (PDE-5) (Huang and Lie, 2013). The process of attaining an erection entails coordination between pathways such as the psychological, neurological, and vascular pathways; these pathways unite to process a physiologic



Fig. 1. Revive capsule

response in the penile vasculature [2]. The pudendal and pelvic splanchnic nerve plexuses send parasympathetic signals to the penile cavernosal tissue, which releases nitric oxide (NO) [3]. This nitric oxide released causes relaxation of the cavernosal smooth muscle and induces a decrease in intracellular calcium; a process mediated by cyclic guanosine monophosphate (cGMP) [4]. When the cavernosal sinusoids are filled, the venous outflow from the penis becomes obstructed as a result of compression of the veins against the tunica albuginea, which permits the maintenance of an erection [5]. The temporary rise in cGMP becomes terminated by phosphodiesterase type -5 (PDE-5), resulting in contraction of the cavernosal smooth muscle rhythmically, thereby inducing a decreased arterial diameter and thus causing venous outflow [6], which eventually leads to detumescence.

These drugs act to inhibit phosphodiesterase type-5, which in turn induces an increase in cGMP levels, and a decrease in intracellular calcium (Ca²⁺), leading to relaxation of the smooth muscle, and dilation of the blood vessels, allowing increased arterial blood flow into the penis, and thus penile erection [7].

3. CONSTITUENT HERBS IN REVIVE HERBAL CAPSULE

3.1 Herba epimedii (particularly *Epimedium sagittatum*)

Herba epimedii (*Epimedium*), which is also called Horny Goat Weed or Yin Yang Huo, is a traditional medicine that originated in Chinese. It belongs to the *Epimedium* species in the family Berberidaceae [8], and has been widely utilized as an important medicine for more than 2000 years, [8]. *Epimedium sagittatum* is one of the five *Epimedium* species recorded in the Chinese Pharmacopoeia Commission [9], and has a widespread in China mainly in the southern, central and eastern areas; usually seen under bushes and in clefts in the natural environment [10].

Epimedium sagittatum has various active components (more than 260 compounds), the major component being the Flavonoids (particularly icariin), which is said to be quality indicators of the *Epimedium* plant in the Chinese Pharmacopoeia [11]. However, in recent times, several studies have reported the presence of four main flavonoids such as icariin, epimedin A,

epimedin B and epimedin C in the *Epimedium* which are thought to be the quality indicators of this plant [12]. The bioactivities or efficacy of the *Epimedium* plant are induced by bioactive components (the prenylated flavonol glycosides) in the plant; these prenylated flavonol glycosides are end-products of flavonol branch of the flavonoid biosynthetic pathway [13]. Flavonoids are notably large group of plant secondary metabolites obtained from phenylalanine, and the biosynthetic pathway of flavonoid is one of the most studied pathways of plant secondary metabolites [14].

The major functions of *Epimedium sagittatum* (or Herba epimedii) were to nourish the viscera of the kidney (as a kidney tonic), and reinforce of masculinity, leading to the restoration of erectile function in men [13]. However, it has also been used to treat several disease conditions such as tumors, osteoporosis, and cardiovascular disease [11,13]. The polysaccharides in the *Epimedium* plant have been shown to possess therapeutic properties against tumor and oxidation; it also increases immunity, and possesses antioxidant properties [15]. Studies have also shown that the metabolic enzyme activities of the liver, such as CYP3A4, CYP1A2 and CYP2E1 (the major isoforms of cytochrome P450) were regulated by epimedii herba extract [10].

3.2 *Radix ginseng*

Ginseng is an herb medicine, used traditionally in China, with at least nine (9) species, which are mostly named on the basis of their geographical origins; *Panax ginseng* (originated from Asia or Korea in Asia, and also called Asian/Korean ginseng), *Panax quinquefolium* (originated from America, and also called American ginseng), and *Panax japonicas* (originated from Japan, and also called Japanese ginseng). The genus name "Panax" is a Greek word, meaning "all-healing", and was named so by a Russian botanist named Carl A. Meyer in 1843.

Several reports have shown ginseng to possess wide-range of physiological activities in several human systems, such as immune, cardiovascular, and neuronal, and has also been used to increase sexual performance and satisfaction. It is commonly taken alone or in combination with an herbal formula to improve sexual performance and treatment of erectile dysfunction. For more than 2000 years now,

Panax ginseng has been applied in traditional Chinese medicine, with its components being proven to exert a wide-range of pharmacological activities [16].

Radix ginseng, which is the dried root of *Panax ginseng*, was reported to calm nerves, stop convulsions, clears the eyes, protect the five visceral organs, tranquilizes the mind and improves memory [17]. It can regulate functions of the central nervous system, endocrine system, cardiovascular system, and immune system [18], (Wee et al., 2011). Also, it promotes metabolism, prevents aging, promotes body growth in children, exert anticancer effects, prevents fatigue, and protects against harm from radiation (Wang et al., 2010). Most interestingly, it was also reported that *Radix Ginseng* functions in the restoration of Yin and Yang, thereby increasing sexual longevity [17].

3.3 *Cordyceps militaris*

Cordyceps is a genus of fungus (mushroom), and a traditional Chinese medicine used in the treatment of various health conditions such as cardiac dysfunction, fatigue, kidney diseases, respiratory, and renal dysfunction [19]. Zhou et al. [20] reported that species of *Cordyceps* are important natural products with diverse biological activities. It grows on caterpillars as a parasitic fungus (that is, it is produced on hosts such as insects) [21], rendering it scarce and costly. It is also implicated in athletic performance, where it first achieved attention in the year 1993, due to the world record-breaking performances of Chinese female athletes after *cordyceps* supplementation. Due to its rareness and high cost, techniques involved in synthetic cultivation have been applied recently for mass generation of this fungus [22].

Cordyceps militaris is a parasite on larvae of moth caterpillar, and is widely used in Eastern part of Asia as a traditional medicine [23], belonging the family Clavicipitaceae. It is used as a health supplement for the promotion of longevity and human health, as well as being utilized as an alternative medicine in the treatment of various disease conditions such as sore throat, cancer, epilepsy, tuberculosis and stroke [24]. However, there are reports of *Cordyceps militaris* being cultivated using an artificial medium rather than being harvested from natural sources while retaining same

bioactive contents and medicinal potential [25].

The *Cordyceps militaris* contains active components such as ergosterol, essential oils, xanthopylls, adenosine, cordycepin, mannitol and polysaccharides, nucleosides, amino acids which possess varying pharmacological effects, including actions against viruses, oxidation, diabetes, platelet aggregation, inflammation and cancer (Yu et al., 2004). It was reported to possess antihypertensive and antiapoptotic properties [26]. Interestingly, it also possesses positive effects in sexual and testicular functions, as demonstrated using rat model [27], and can therefore be used in treating erectile or sexual dysfunction in men.

3.4 *Tribulus terrestris* (Also Called *Fructus tribuli*)

The genus *Tribulus* belongs to the family Zygophyllaceae, and constitutes about twenty (20) different species worldwide, out of these, three (3) species are commonly found in India; these species include *Tribulus cistoides*, *Tribulus terrestris*, and *Tribulus alatus* [28]. Among all the species, *Tribulus terrestris* is the most used by herbalists and Ayurvedic seers owing to its medicinal properties [29]. It is a yearly shrub occurring in subtropical, Mediterranean, and desert climate regions such as southern USA, India, China, Spain, Bulgaria, and Mexico. The plant may be used alone or in combination with other compound formulations for therapeutic purpose or for the supplementation of foods [29].

Tribulus terrestris is a common weed found in very hot, dry and sandy regions or waste places, such as the pasture lands and road sides. It is usually known as puncture vine, land (or small) caltrops, and is distributed all over India [30]. Phytochemical analysis revealed that the plant contains tannins, glycosides, saponins, alkaloids and flavonoids [31]. However, the content and composition of saponin in *Tribulus terrestris* differ between from different geographic regions [32].

The plant is used in traditional medicines for several purposes, including diuretic, astringent, aphrodisiac, urinary disinfectant, antihypertensive, tonic and stomachic. Disorders of the genito-urinary tract are effectively treated using the dried fruit of this

herb, and also to remove urinary stones [33]. For centuries now, the plant has also been used in Ayurveda for the treatment of erectile dysfunction or impotence, venereal diseases, and sexual weakness; the root fruits of this plant are also said to possess cardio-protective properties. Furthermore, the fruits have been utilized in the treatment of abnormal morbid leucorrhoea, eye function, edema, and distension of the abdomen, and sexual dysfunction. It is also used to restore depressed liver, and to treat mastitis, flatulence, acute conjunctivitis, headache, and vitiligo [34].

The extract of this plant was reported to have exerted a pro-erectile effect on the corpus cavernosum smooth muscle of rabbit after oral treatment for eight weeks [35]. Also, there was a significant elevation in serum testosterone levels after the use of *Tribulus terrestris* as a sexual enhancer in the management of sexual dysfunction in men [36]. Furthermore, the ethanolic extract of *Tribulus terrestris* showed a protective effect against testicular damage induced by cadmium, and this protective effect may be attributed to the inhibition of peroxidation of testicular tissue, chelating of antioxidants and metals or through the stimulation of testosterone production from the Leydig cells [37].

3.5 *Radix polygoni multiflori*

Radix Polygoni Multiflori is the dried root tuber of *Fallopia multiflora* or *Polygonum multiflorum* (Thunb.), and belongs to the family Polygonaceae [38]. *Fallopia multiflora* is a species of flowering plant, known as fleecyflower and Chinese knotweed, and commonly found in southern and central China.

The raw *Radix Polygoni multiflori* is said to possess anti-toxicity property, treats carbuncles, and helps in the relaxation of the large intestine [39]. On the other hand, the processed form of this plant ameliorates or protects the liver and kidneys, colors the hair black and helps to make the tendons and bones strong. It also possesses hypolipidaemic activity, and used to treat anaemia and weakness of the lumbar [9]. Some drugs (containing *Radix Polygonum multiflorum*) commonly used in China to treat fatty liver and hyperlipidaemia have obtained

approval by the Chinese Food and Drug Administration; this is because *Radix Polygonum multiflorum* gives vitality to the liver and kidneys [40].

The major active ingredients of *Radix Polygonum multiflorum* are flavonoids, anthraquinones, phospholipids, phenols, and stilbenes; stilbene glycosides, emodin and physcion are said to be the major ingredients with hypolipidaemic property [41]. Raw *Radix Polygonum multiflorum* have pharmacological properties different from processed *Radix Polygonum multiflorum*. The processed plant probably has lower content of anthraquinones glycosides, while the raw has higher content, and as such, the latter inhibits the accumulation of triglyceride induced by carbon tetrachloride (CCl₄), and also promotes immune activities and anti-immunosuppression [42]; these activities may be attributed to the presence of high anthraquinones glycosides content. Zhao et al. [43] also reported a reduced liver enlargement caused by CCl₄.

3.6 *Eucommia ulmoides* (Also Called *Cortex Eucommiae*)

Eucommia ulmoides (EU) is commonly referred to as "Du Zhong" in Chinese language. The genus *Eucommia* belongs to the family Eucommiaceae, which is a small tree mainly found in Central China, and widely cultivated in on a large scale owing to its medicinal relevance [44]. It grows well in strong light conditions, and on altitudes of 300-2500 meters range and yearly rainfall of about 1000 millimeters, and is appropriate for growing in sandy/humus soils containing a pH range of 4.5-8.0. It can withstand extreme temperatures of 44°C (high) and -40°C (low) [45].

Eucommia ulmoides contains several active components, out of which about 112 have been isolated; some of these isolated components include flavonoids, steroids, lignans, phenolics, and iridoids. This plant has shown some medicinal properties; the leaf possesses increased activity related to the cortex, flower, and fruit [46]. Interestingly, reports stated that the leaves of this plant promote bones strength and body muscles [47], thus resulting in longevity and enhancing fertility in humans [48]. Reports states that the flavonoid compounds (such as rutin, chlorogenic acid, ferulic acid, and caffeic acid)

present in the leaves of the plant exerts antioxidants property [49]. Also, delicious tea formula obtained from the same leaf of *Eucommia ulmoides* was said to reduce fat and promote energy metabolism [50].

Furthermore, the plant *Eucommia ulmoides* serves as a tonic to the liver and kidneys, and strengthens muscles and bones. Also, reports have it that, the plant has potentials that treat hypertension, hyperlipidemia, fatigue, diabetes, oxidative degradation, and inflammation. It also protects the neurons, liver, and kidney, and prevents aging and depression, regulates the immune system, induces relaxation of the smooth muscle of the uterus, and enhances penile erectile function [51].

The plant *Eucommia ulmoides* Oliv induces regulatory effects against endothelial nitric oxide synthase uncoupling which promoted nitric oxide release, thus enhancing penile erection, and can therefore be used to treat erectile dysfunction. However, the high content of active compounds such as asperulose, geniposidic acid, quercetin, chlorogenic acid, and aucubin plant, particularly in the leaves is used possess a hypolipidemic potential [52]. Several studies also suggested the hepatoprotective potential of *Eucommia ulmoides* on liver damage in rats, and it revealed that treatment with *E. ulmoides* Oliv extract induced a decrease in the AST, ALT, ALP and lactate dehydrogenase (LDH) levels in serum [53].

4. PHYTOCHEMICAL COMPONENTS OF REVIVE HERBAL CAPSULE

4.1 Flavonoids

Flavonoids are a very essential group of natural materials belonging to a class of plant known as secondary metabolites that possess a structure resembling that of polyphenols; they are generally present in beverages, fruits and vegetables [54]. Flavonoids possess both anti-oxidant and biochemical potential related to several diseases such as cancer, Alzheimer's disease, and atherosclerosis [55,56]. Flavonoids produce certain effects which promote health, and their applications cannot be replaced in nutraceutical, pharmaceutical, medicinal and cosmetic; this may be attributed to their anti-oxidative, anti-inflammatory, anti-

mutagenic and anti-carcinogenic potentials together with their ability to mediate key cellular enzyme functions. Also, they are potent inhibitors for several enzymes, including xanthine oxidase (XO), cyclooxygenase (COX), lipoxygenase and phosphoinositide 3-kinase [57,58].

Flavonoid compounds are part of a class of phenolic compounds with low molecular weight, and are widely-spread in the plant kingdom. They are found in several parts of plants, and are extracted from the plants. Vegetables make use of these flavonoids to promote their growth and defensive mechanisms against plaques [59]. In most angiosperm families, many flavonoids are easily seen and recognised as flower pigments, however, they do not occur only in flowers but are also found in every part of plants [60]. Flavonoids are also found in large amounts in foods and beverages made from plant, including wine, fruits, cocoa, tea and vegetables, therefore, they are referred to as dietary flavonoids [60].

There are several subgroups of flavonoids including isoflavones, flavones, flavonols and chalcones; these subgroups have main sources that are unique, for instance onions and tea are main dietary sources of flavones and flavonols. Flavonoids function in different biological activities in plants and animals, likewise in bacteria. In plants, they are produced in specific areas and account for the aroma and colouration of flowers [61]. In fruits, they are responsible for the attraction of pollinators and consequently dispersion of fruits to enhance the germination of seed and spore, and thus promote the seeds to grow and develop [62]. Flavonoids proffer protection on plants from different biotic and abiotic stresses, and also function as unique ultraviolet filters [63]. They also act as phytoalexins, signal molecules, detoxifying agents, allelopathic compounds, and defensive compounds for anti-microbial. They play essential functions by preventing frost to become hard and resist drought, and may also function in the acclimatisation of plant heat and the tolerance of freezing [64]. Also, flavonoids exert positive effects on humans' and animals' health, by being efficient when used to treat diseases and also prevent diseases. Presently, approximately six thousand flavonoids exist, contributing to the

colour pigmentation of medicinal plants, vegetables, herbs and fruits [65].

4.2 Cardiac Glycosides

Cardiac glycosides are chemical compounds used to poison livestock, and to treat congestive heart failure [66]. The latexes or extracts of cardiac glycosides of plants are said to be used in the poisoning of arrows in South America, Africa, and Asia to hunt and fight; therefore, it is speculated to have emerged as a defensive mechanism in plants. They are steroids with the potential of exerting certain effect on the muscle of the heart, in that; a very little quantity can exert a useful effect on a heart that has been diseased. They stimulate an increase in the contraction of cardiac muscle without a simultaneous increase in oxygen consumption; as a result of this action, the heart muscles become more efficient in pumping, and are thus capable to meeting the demands of the circulatory system [67,68].

They are a set of plant component consisting of two major groups of compounds that vary in their aglycone's structure. They are either 23-carbon or 24-carbon steroids having a basic nucleus of cyclopentanoperhydrophenanthrene substituted at carbon-17. The first class called Cardenolides bears a lactone group made of five members in the carbon-17 with α , β -unsaturated γ -lactone ring (butenolide), while the second class called bufadienolides was discovered primarily as poisons in the skin of toads; these two classes can be produced by plants. Minor class of cardiac glycoside, such as isocardenolides, bears the double-bonded butenolid ring at the 21st and 22nd position rather than the 20th position. However, clinically the cardenolides are mostly relevant, and this may be attributed to their therapeutic utilization. Some isocardenolides may not possess any potential to exert effects of the heart [69].

Both classes of cardiac glycosides possess a structure, solubility and foaming characteristics similar to that of steroid saponins; they are differentiated from other steroid glycosides due to the presence of 14-hydroxy group with their skeleton having some unique sugar. The sugar residues are always attached at carbon-3, meanwhile in some members, an aldehyde group is attached at the carbon-19, and not a methyl group [70]. Cardiac glycosides are of more abundance than aglycones. However, some aglycones present in cardiac glycosides are

useful for the treatment of congestive heart failure; the commercially available aglycones include strophanthidin, digoxigenin, ouabagenin and gitoxigenin, while the most commercially essential cardiac glycosides from plants include *Digitalis purpurea*, *Strophanthus gratus*, *Strophanthus kombé* and *Digitalis lanata* [71]. Mostly, the sugar residues are linked to the aglycone at carbon-3 via β -linkage, and are made up of about four residues of sugar; the attached sugar may be rhamnose or glucose combined with other deoxy sugars that are in association with only cardiac glycosides [72]. Cardiac glycosides are found in small quantities in most parts of plants including the bark, seeds, stems, roots, and leaves, and are widely distributed [73].

Among others, the most essential usefulness of the cardiac glycosides is its action and effectiveness when used to treat cardiac failure. When there is cardiac or congestive heart failure, the heart is unable to pump enough blood as needed by the body. In every heart muscle contraction, an influx of sodium ion, and an outflow of potassium ion takes place, such that before the time for next contraction, the concentration gradient that pumps sodium ion into the cell against the gradient of the concentration, which must first be re-established by the Na^+ , K^+ -ATPase; energy is needed for this process to occur, and this energy is generated from the hydrolysis of adenosine triphosphate to adenosine diphosphate by the Sodium ion, Potassium ion-ATPase [68]. However, cardiac glycosides act by inhibiting the Sodium ion, Potassium ion-ATPase, with consequent elevation in the myocardial contraction force [68].

Digitalis is a cardiac glycoside derived from plants. It is frequently used to treat chronic heart failure, atrial fibrillation, and re-entrant supra-ventricular tachycardia [74]. In the United States however, Digoxin happens to be the only available preparation of digitalis. Some flowering plants, such as oleander and lily-of-the-valley contain cardiac glycosides. However, toxicity resulting from cardiac glycoside occurs as a result of ingestion of some plants, including foxglove and yellow oleander (*Thevetia peruviana*); also, a similar toxidrome is related with the use of herbal dietary supplements containing cardiac glycosides. One of the most prescribed drugs in the United States is Digoxin [75].

4.2.1 Mechanism of action of cardiac glycosides

Cardiac glycosides including digoxin induce a direct vasoconstriction in the arterial and venous system in vascular smooth muscle. The inotropic effect of digitalis occurs when the membrane-bound sodium- and potassium-activated adenosine triphosphatase (Na^+/K^+ -ATPase) is directly inhibited by the drug, leading to a rise in the intracellular concentration of calcium. It begins with the binding of digitalis specifically to the Na^+/K^+ -ATPase, inhibiting its enzymatic activity, and impairing active transport of extruding sodium and transport of potassium into the fibers (in a ratio of 3:2). This results in a gradual increase in intracellular sodium, and a gradual, little decrease in intracellular potassium. Cardiac fiber calcium (intracellular calcium) is exchanged for extracellular sodium (in a ratio of 3:1) by a transport system that is driven by the concentration gradient for these ions, and also by the potential across the membrane. Therefore, the increased intracellular sodium ion is associated with the positive inotropic effect of digitalis [76]. The increase in intracellular sodium ion leads to an accumulation of intracellular calcium through the sodium ion-calcium ion ($\text{Na}^+/\text{Ca}^{2+}$) exchange system. Furthermore, in the heart, the increased intracellular calcium induces the release of more calcium from the sarcoplasmic reticulum, thus providing more

calcium available to bind troponin C, and increasing contractility of the cardiac muscle. Also, the increased intracellular calcium is accompanied by a low pH, which then results in the activation of a Na^+/H^+ exchange pump, leading to extrusion of hydrogen ion and an intrusion of sodium ion, causing greater contractility [76].

4.3 Tannins

The nomenclature 'tannin' is obtained from the French name 'tanin' (a tanning substance), and is used for different natural polyphenols. The definition of tannins by Bate-Smith and Swain states that, they are phenolic compounds with a molar mass ranging between 300 and 3000, that are soluble in water, putting into consideration the phenol reaction (blue colour with iron chloride), and also precipitating alkaloids, gelatins and other proteins. Unfortunately, this definition does not consider all tannins; this is because, recently, molecules possessing a molar mass of up to 20000 daltons have been discovered, which should also be classified as tannins based on their molecular structures. Then, Griffith came up with a definition that, tannins are "macromolecular phenolic substances"; he went ahead to divide them in two major groups, namely the 'hydrolysable' and 'condensed' tannins [77].

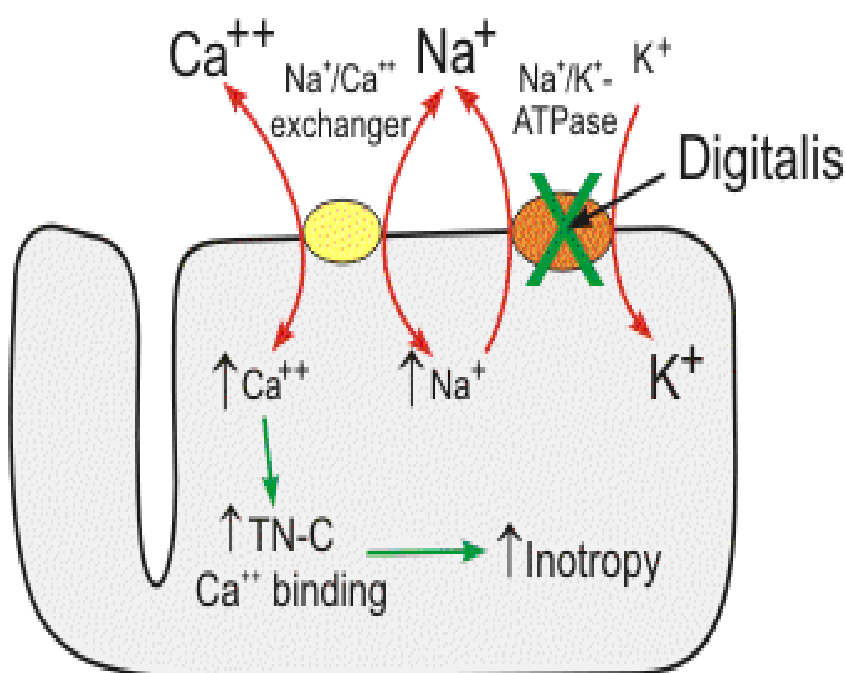


Fig. 2. Mechanism of action of cardiac glycosides

For several decades, it has been established that certain organic substances possess tanning potentials, with the ability to tan animal skins to obtain leather. However, with the aid of modern analytical techniques in the twentieth century, what happened during the tanning process was properly explained; in real tanning, cross-linking of the skin's collagen chains occurs, while in false tanning, the hollow spaces between the skin's collagen chains are filled. However, mineral tanning (represented by alum tanning, and recently by chromium tanning) has replaced the traditional tanning of animal skins [77].

Tannins are present globally in most families of the higher plants, for example in Sumach, oak wood and chestnut; also, they have a varying chemistry. Almost every part of the plant contains high concentrations of tannin, such as in the wood, seed, bark, fruit and leaves. An elevated production of tannin may be related to sicknesses, thus it can be stated that the biological action of tannin in most plants is associated with protection against insects or infection, or act as an animal herbivore. The appearance of tannins is light-yellow or white-amorphous. They are powders or shiny, almost colorless, loose masses, characterized by a strange smell and astringent taste. They are applied in industries, medicine and food industries particularly in Asia, where they are used (the plant extract) to treat stomach and duodenal tumors, inflammation, and diarrhea, and also used as diuretics and antiseptics [77].

Tannins have the ability of precipitating heavy metals and alkaloids (except morphine), as such, they can be utilized in poisonings with these substances [78]. They are also useful in dyestuff industry, where they are used as caustics for cationic or tannic dyes, and also used to produce inks. Tannins are used in the food industry to clarify fruit juices, wine and beer. In industries, they can also be used as textile dyes, coagulants in rubber production, and as antioxidants in wine, beer and fruit juice. In recent however, tannins have really been noticed scientifically, particularly due to the raised incidence of deadly diseases such as AIDS and several cancer types. Many types of tannins possess anti-tumor, antiviral, and antibacterial potential; certain tannins possess the ability to selectively inhibit HIV replication [77].

4.4 Quinones

Quinones are a type of secondary metabolites derived from plants. They constitute a class of

compounds bearing the quinone structure, and can be divided into four major types: phenanthrenequinone, benzoquinone, anthraquinone and naphthoquinone based on the number of benzene rings in the structural skeleton [79]. They are well-distributed in the plant kingdom and exist mainly in higher plants; for example among others, those from the families of Leguminosae, Polygonaceae, Rhamnaceae, Labiatae, Boraginaceae, and Rubiaceae [79]. Several quinones possess significant biological potential, including the purgative effect of quinones obtained from *Rheum officinale* L., the antibacterial action of juglone obtained from *Juglans mandshurica* Maxim, and the anti-cancer action of plumbagin obtained from *Plumbago pearsonii* L. Bolus [80,81]. There are over 1,200 quinones in nature [82], with a basic structure that is common, which is either a para- or an ortho-substituted dione combined, forming either a nucleus which is aromatic (to form benzoquinones) or a polycyclic aromatic system that is condensed.

Quinones may as well be found in little quantity in animals, particularly in echinoderms, and also in bacteria and fungi [83]. However, some quinones are toxic; examples include anthraquinone and 1-hydroxyanthraquinones, which can be produced in the environment through a process of photo-oxidation of contaminants in the environment by sunlight [84]. They possess essential biologic functions, such as the enhancing photosynthesis in plants and bacteria [85]; their use of coenzyme Q in anti-oxidative action, membrane stabilization, and prevention of cellular damage due to normal metabolic processes, and protection against chronic diseases, such as Parkinson's and cardiovascular diseases [86,87,88].

4.5 Alkaloids

Alkaloids are compounds that contain nitrogen, and are of low-molecular-weight. They contain different cyclic rings bearing an atom of nitrogen, which is usually alkaline in nature. The metabolites may be divided into various classes on the basis of their precursor, and there are over twenty different classes of alkaloids [89].

Alkaloids and other secondary metabolites found in plants promote the rate of reproduction in plants, through the improvement in defenses against biotic and abiotic stresses or through the enhancement of pollinators and visitation of seed/fruit disperser [90]. Some of the defensive

mechanisms used by alkaloids include repellence of predator through being toxic or being having a bitter taste, or through repair of damage by the antioxidant system [91,92]. Visitors of flower may be attracted by the stimulant potentials of some alkaloids, while duration of visit may be regulated by non-fatal toxicity [93]. This metabolic versatility of alkaloids result in significant improvement in the rates of survival for plants and also provide essential pharmacological actions for the therapeutic potential including antioxidant, anti-tumoral, analgesic, and anti-inflammatory effects [89].

Alkaloids are one of the most essential drugs in the history of human's existence. The major function of alkaloids in plants is being toxic against pathogens and predators, which is used as the plant defense mechanism [94]. However, the same toxic effects seen in the plant defense mechanism may be used to prospect new drugs. For example, certain tumor cell types may be fought, or specific microorganisms may be controlled using a very specific toxicity of the plant [89].

Alkaloids can be applied in medicine, therapy, recreational, and religious settings. Plant alkaloids from different classes have been used to change senses due to their ability to modulate the human central nervous system. Centuries ago, it was believed that Tropane alkaloids obtained from several species of Solanaceae have been utilized by witches in the practicing sorcery [95]. In recent times, alkaloids which are toxic or have the potential of being toxic are used; they include tea, foods or beverages containing caffeine (mainly *Camellia sinensis*), which are used to achieve mental alertness, and for enhancement of physical training. Others include nicotine (which may be present in pipes, cigars and cigarettes) [96], which stimulates the central nervous system; morphine which is a very effective analgesic; codeine which is a sedative and cough suppressant; and cocaine and other illicit psychoactive drugs [95]. For the management of crops, alkaloids capable of causing low toxicity in humans may be advantageous by taking off herbivores. For instance, the *Lupinus* species has a relatively increased amount of the quinolizidine alkaloid, and are therefore less palatable; thus, the plant species requires less pesticide application [91].

Animal intoxication by alkaloids occurs mainly due to accidental ingestion of foods contaminated with plants containing alkaloids.

Some alkaloids pose extreme harm to mammals, such as in the case of the alkaloid cycloamine (which is a steroid) in lambs, was said to be obtained from the plant *Veratrum californicum*, and is responsible for teratogenicity leading to craniofacial birth defects in the offspring of sheep that grazing *V. californicum*. Some plants that contain tropane alkaloids, have been utilized in medicine owing to their strong hallucinogenic and anti-cholinergic actions, inducing vision disturbance, constipation, photophobia, inducing the upper digestive tract and respiratory tract mucosa to dry, and pupil dilatation. Poisoning resulting from solanine ingestion primarily induces disorders of the gastrointestinal and neurological systems [91].

Consumption (via foods, beverages and supplements) of alkaloids promotes nutrition, immune functions, and physical performance [97]. For example caffeine from coffee possessing antioxidant, anti-inflammatory, and stimulatory potentials; and shogaols and gingerol (which are phenolic alkanones) found in ginger with potentials against inflammation, microbes, oxidation, and tumor [95].

In animals, alkaloids affect different metabolic systems, with considerably varying toxic mechanism of action [98]. The toxicity may occur due to enzymatic alterations which may have affected physiological processes, DNA synthesis inhibition and DNA repair mechanisms, or effects on the nervous system. Toxic effects due to pyrrolizidine alkaloid may occur primarily due to their ability to become bio-transformed into pyrrole structures (that are strongly reactive) catalyzed by oxidases present the liver of mammals. These reactive pyrroles function by triggering the alkylation of nucleic acids and proteins [99].

4.6 Polyphenols

Foods obtained from plants naturally contain polyphenols, which are a group of biologically active compounds that possess several complex structures. The phenolic ring is the basic monomer in polyphenols, and depending on the phenolic ring's tensile strength, the polyphenols may be arranged into several groups, with the major groups being stilbins, phenolic acids, phenolic alcohols, lignans and flavonoids [100]. Polyphenols being the biologically active compounds are embedded in humans' diet such as cereals, fruits, vegetables, and

coffee; also, they prevent degenerative diseases because most frequently-occurring antioxidants in the diet are obtained from polyphenols [100].

The anti-oxidant potential of polyphenols prevents the oxidative change in LDL, which is the primary mechanism in the formation of lesions in the endothelium occurring in atherosclerosis [101,102]. Polyphenols also play a role in the treatment of diseases such as neurodegenerative disease, cardiovascular disease, osteoporosis, diabetes mellitus and cancer [101]. Several fruits, vegetables, kale, onions and broccoli are rich in polyphenols [103].

There are two groups of phenolic acids namely hydroxycinnamic and hydroxyl-benzoic acids; hydroxybenzoic acids contributions to the diet of humans diet are very rare, and this may be the reason they are not been suggested to have played a role in the health of humans. Phenolic acids have the bound and unbound (free) forms; the bound forms are found in hull, bran, and seed, while the unbound (free) forms are found in vegetables and fruits [104,105]. Flavonoids are composed of two rings of benzene; these rings may be bound to 3-carbon chain from the surrounding pyran ring. There are about 6 different classes of flavonoids which vary one another, mainly on the basis of central carbon's oxidation state; these six classes include anthocyanidins, flavanones, isoflavones, flavanols, flavones, and flavonols. Over four thousand flavonoids have been discovered from plant sources. In flavonols, the double bond occurs between carbon-3 and carbon-2, with a hydroxyl group that is attached at carbon-3. Most flavonoids in several food sources are flavonols, with onions being the main supply of flavonols [106]. Also, coverings of fruits contain flavonols because light activates their production; even on the same piece of fruit, the flavonol content differ due to exposure to light at their different edges [101]. However, flavones are found in abundant amount in the peel or skin of fruits. At carbon-4, flavanones possess an oxygen molecule, and are basically attributed by a three-carbon ring that is saturated. The main source of flavanones is citrus fruits (in the rigid parts of fruits and fruit coverings), but flavanones are also found in aromatic plants [101].

Isoflavones are similar to estrogens; owing to the presence of the hydroxyl group between

carbon-4 and carbon-7. These are referred to as phyto-estrogens because of their estrogen receptor-binding potential, and are abundant in soy and its products. Anthocyanins are colorants with hydrophilic property, for example vegetables and fruits show red or blue colour due to these pigments. They occur primarily in anthocyanidins form with sugar moiety at carbon-3, 5 [101].

Polyphenols depend mainly, on their bioavailability to exert their biological effects, and their chemical structure determines their limit and rate at which they are absorbed via the intestines [107]. In developed countries, main factors for death in countries that are developed countries are coronary heart disease and stroke [108]. The development of cardiovascular disease is based on both environmental and genetic factors, and some risk factors for cardiovascular disease include lack of exercise, smoking, and saturated fat intake [109]. However, there was an inverse correlation between coronary disease and ingestion of flavanols, flavonols, and flavones [110]. Also, Mink et al., [111] reported a reduced cardiovascular-related death as a result of ingestion of flavanones and anthocyanins. The antioxidant property of polyphenols is said to be related to their cardioprotective potentials; this is as a result of decreased blood pressure [112], with enhanced endothelial tissues function [113], with the inhibition of platelets aggregation [114] by the decrease in the oxidation of LDL [115] and by decreasing the inflammatory response [116]. Polyphenols play a protective role on the heart by enhancing the action of nitric oxide synthase, and promoting the bio-availability of nitric oxide for use by the endothelium [117]. Studies revealed that relaxation of the endothelium has been observed through the consumption of polyphenols [118].

5. CONCLUSION

Due to the high cost of western drugs, and many accompanied side effects, most individuals especially of African origin have consented to using herbal/traditional drugs which are relatively cheap and affordable with fewer or no side effects. Revive capsule is absolutely natural, obtained from a mixture of several herbal constituents of specific doses. This drug is widely used in the entire globe particularly in Africa and

Asia, for the treatment of erectile dysfunction or enhancement of libido, and may thus be referred to as an herbal phosphodiesterase type-5 inhibitor; the mechanism of action of which may be attributed to the contained phytochemicals which are known to be the bioactive ingredients of the drug.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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