# Molecular Action of Herbal Medicine in Physiology of Erection and its Dysfunction

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**Abstract.** Erection is a physiological process that involves vascular, hormonal, and nervous factors. Erectile dysfunction is one of the male sexual problems that occur globally and is reported to affect men's quality of life. Herbal plants have been widely used for disease treatment, including the problem of erectile dysfunction. This paper aims to review the molecular potential of various plants in the physiology of erection and to treat erectile dysfunction. The literature search was carried out through the Pubmed and Google Scholar databases regarding the molecular mechanisms of herbal plants and their potential involvement in the physiology of erection and overcoming erectile dysfunction. This paper focuses on six herbal plants: *Panax ginseng, Ginkgo biloba, Epimedium,* Black pepper*, Tribulus terrestris,* and *Eurycoma longifolia*. The six herbal plants have involvement in the erection process and have molecular potential in the treatment of erectile problems

## 1 Introduction

Penile erection is a complex physiological process involving neurological, vascular, and humoral factors. This cascade is triggered by auditory, visual, olfactory, and local stimuli in the penis, increasing the flow of the pudendal artery, followed by dilatation of the cavernous arteries and helicine arterioles. This process causes smooth muscle relaxation, allowing blood accumulation in the penile corpora [1]. Disruption of this physiological process can lead to various sexual problems, one of which is erectile dysfunction. Erectile dysfunction [ED] is one of the sexual problems where a man is unable to get an erection or maintain the penis rigidity to reach expected sexual intercourse [2].

The pathophysiological process of ED involves vascular, neurological, psychological, and hormonal factors [3-5]. The global prevalence of ED is estimated at 3-76.5% [6] and is often associated with various conditions, including cardiovascular disease [7], diabetes mellitus [8], and obesity [9]. Studies reported that sexual problems, including ED, can affect relationship happiness and reduce sexual satisfaction in both men and women [10]. The study conducted by Agaba et al. showed that the ED condition significantly affects men's social function and negatively affects their quality of life [11].

Patients with ED carry out efforts to seek treatment to overcome this sexual problem, one of which is by utilizing herbal plants, which are believed to be passed down from generation to generation to overcome health problems, including sexual problems. Research on herbal medicine is growing, including its use to support physiological processes in the human body and overcome sexual problems. It is known that more than 718 plant species are used as aphrodisiacs and have the potential to overcome sexual problems such as decreased libido and erectile dysfunction [12, 13].

We conducted a literature review of several studies related to herbal plants in overcoming erectile problems. This paper discusses the molecular potential of six herbal plants, namely *Panax ginseng, Ginkgo biloba, Epimedium,* Black pepper*, Tribulus terrestris,* and *Eurycoma longifolia,* as alternative therapies for erection problems.

## 2 Methods

This study is a literature review that serves as a prelude to a systematic review that aims to identify the available evidence regarding the molecular involvement of various types of herbal plants in the erection process and their potential involvement in treating erectile problems. We conducted a literature search on the PubMed and Google Scholar databases using keywords such as "physiology of erection"; "molecular mechanism of erection"; "pathophysiology of erectile dysfunction"; "corpus cavernosum"; "nitric oxide"; "molecular pathway"; "Panax ginseng"; "Ginkgo biloba"; "Epimedium"; "Black pepper"; "Tribulus terrestris"; "Eurycoma longifolia".

## 3 Physiology of erection

The penis consists of three parts: a pair of corpora cavernosa and a part of the corpus spongiosum. The corpora cavernosa consists of tunica albuginea, collagenous sheaths composed of variously sized

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sinusoids supported by a fibrous skeleton. The fibrous skeleton has the role of structural support and is compounded of tunica albuginea surrounded by smooth muscle trabeculae, elastic fibers, and collagen. Because of the composition allows blood to fill the sinusoids of corpora cavernosa and maintain rigidity during an erection [14].

Penile erection is a physiological process that can occur spontaneously or following sexual stimulation. The penis undergoes enlargement due to increased blood flow to the corpora cavernosa and corpus spongiosum. The penile erection involves a complex interaction of vascular, neurological, and molecular factors and is modulated by hormonal factors [15-18]. In most cases, a penile erection occurs due to sexual stimulation that can trigger inhibition of sympathetic activation of parasympathetic and release of pro-erectogenic neurotransmitters from cavernous nerves [14]. Intracellular calcium levels will decrease due to parasympathetic nerve activation, which leads to relaxation of cavernosal and arterial smooth muscle. Blood flow in the corpora cavernosa sinusoids will increase by about 20-40 times. Enlargement of this sinusoid will cause blood flow out of the vein to be blocked by the corpora near the tunica albuginea. The sinusoids and the inelastic portion of the tunica albuginea compress the vein to help maintain penile tumescence [14].

## 4 Molecular mechanism of penile erection

The extent of sexual stimulation is a factor that plays an important role in the transition of penile rigidity due to the contraction of erectile tissue and erection when the erectile tissue undergoes relaxation. One of the neurotransmitters that play an important role in the process of penile erection is nitric oxide [NO]. Nitric oxide is produced from amino acid L-arginine by neuronal nitric oxide synthase [nNOS] and endothelial nitric oxide synthase [eNOS] catalyzation that is located in the neurons and endothelial cells [19].

NO synthesized will undergo diffusion in smooth muscle cells. This diffusion process will make NO bind to guanylyl cyclase [GC], which will stimulate an increase in cyclic guanosine monophosphate [cGMP] and activation of protein kinase G [PKG]. This process causes phosphorylation of several intracellular proteins and ion transporters, resulting in hyperpolarization and a decrease in Ca2+ in the cytoplasm leading to smooth muscle relaxation [20]. A reduction of Ca2+ concentration causes dephosphorylation of myosin light chain [MLC] by myosin light chain phosphatase [MLCP], resulting in the release of myosin from actin and smooth muscle relaxation [20, 21].

Due to neuronal stimulation, cyclic adenosine monophosphate [cAMP] is also involved in the erection process. Neuronal stimulation initiates an increase in intracellular calcium and activation of adenylate cyclase [AC], which in turn causes an increase in intracellular cAMP. This increase in cAMP results in activation of PKA so that nNOS in Ser-1412 becomes phosphorylated. Another impact of PKA activation is an increase in the catalytic activity of nNOS [22, 23].

## 5 Molecular pathophysiology of erectile dysfunction

Erectile dysfunction can occur due to various factors such as psychological disorders and aging, leading to diseases such as cardiovascular disease and diabetes mellitus [DM] [24, 25]. These factors contribute to the development of erectile dysfunction through various molecular signaling pathways, including the nitric oxide [NO]/cyclic guanosine monophosphate [cGMP] pathway, increased production of reactive oxygen species [ROS], renin/angiotensin system [RAS], RhoA/ Rho-associated protein kinase pathway, and tumor necrosis factor-alpha [TNF-α] pathway [24].

Oxidative stress is an important factor in the pathophysiology of various diseases, including erectile problems. Increased oxidative stress such as NADPH oxidase complex [NOX] will trigger ROS formation and can cause a decrease in NO bioavailability [26].

Erectile dysfunction is a common condition in men with hypertension and diabetes. In the case of hypertension, there will be an upregulation of RAS activity through its main effector, Angiotensin II [Ang II], which leads to endothelial dysfunction [27]. The effect of increasing Ang II on ED was confirmed by a study conducted by Baumhakel et al. by performing intracavernosal Ang II injection, which caused the termination of erection [28]. The mechanism of action of Ang II on the angiotensin receptor type I [AT1] results in an increase in intracellular calcium. This condition is followed by inhibition of myosin light chain phosphatase, which increases oxidative stress and decreases NO bioavailability in cavernosal smooth muscle. This series of events became the critical cause of increased muscle tone to maintain penis flaccidity [27].

Another risk factor for ED is the aging process, as in the results of research conducted by Ding et al., which stated that increasing age would result in a significant decrease in eNOS protein expression and an increase in Rho-kinase [ROCK] protein level [29]. ROCK is a major downstream effector of RhoA, which plays a critical role in regulating the actin-myosin contraction process [30, 31]. Changes in RhoA/ROCK activity in the penis will lead to erectile problems [32].

Endothelial dysfunction is a critical factor in the pathophysiological process of erectile dysfunction, mainly due to inflammation and oxidative stress. Elevated plasma TNF-α levels are one of the leading conditions for vascular endothelial dysfunction. TNF-α is also a triggering factor for ROS formation that can cause suppressive effects of eNOS through destabilization of eNOS mRNA in endothelial cells, which can further reduce NO production [33-37].

## 6 Herbal medicine in the physiology of erection and its dysfunction

### 6.1 *Panax ginseng*

Ginseng belongs to the Araliaceae family, and the genus *Panax* is a herbal plant widely used for medicine, especially in Korea, China, and Japan. In addition to the root, ginseng is commonly used in extract form. It is believed to be useful for reducing stress and fatigue, as an energy-boosting supplement, and as anti-aging [38-40]. *Panax ginseng* is one of the 17 species of Panax most often used for food and medicine [41]. Several therapeutic potentials of ginseng have been reported, including as an anti-inflammatory agent [42], antioxidant agent [43], and potentially overcome sexuality problems [44, 45].

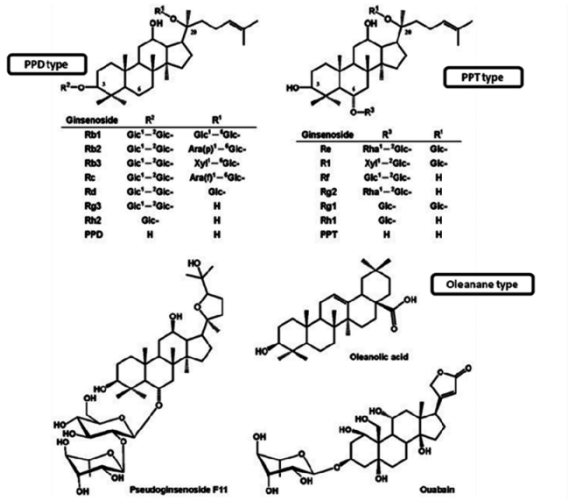


**Fig. 1.** Chemical structure of ginsenosides [48]

*Panax ginseng,* one of the species most commonly used for medicine, contains the active component ginsenosides [Figure 1], which have been extensively studied [46-48]. There are approximately 200 ginsenosides including major ginsenosides [Rb1, Rb2, Rc, Rd, Re, Rg1, etc.] and minor ginsenosides [Rg3, Rh1, Rh2, etc.] [49].

Ginsenosides have been shown to stimulate NO production in several systems. Rb1 inducing NO production in human aortic endothelial cells. The previous study showed that Rb1 affects eNOS phosphorylation at Ser-1177 in a concentration-dependent manner [50].

A previous study by Leung et al. found that Rg1 increased the phosphorylation of glucocorticoid receptor [GR], phosphatidylinositol-3 kinase [PI3K], Akt/PKB, and eNOS leading to increase NO production in human umbilical vein endothelial cells [HUVECs] [51]. Another study by Wang et al., 2010 identify the effect of ginsenoside Rg1 on the underlying molecular mechanism of copulatory behavior of male mice. A total of 10 mg/kg BW Rg1 was injected intraperitoneally, and testosterone, NO, and cGMP levels in the corpus cavernosum were examined. The results showed increased serum testosterone concentration, increased NO release, and accumulation of cGMP in the corpus cavernosum based on in vivo and in vitro examination [52].

Ginsenoside Rg3 was reported to have an inhibitory effect on corporal phosphodiesterases [PDE] in a concentration-dependent manner. This inhibitory effect resulted in an increase of cyclic adenosine monophosphate [cAMP] and also cyclic guanosine monophosphate [cGMP] in corporal smooth muscles [53]. This indicates the potential of *Panax ginseng* in overcoming erectile dysfunction.

### 6.2 *Ginkgo biloba*

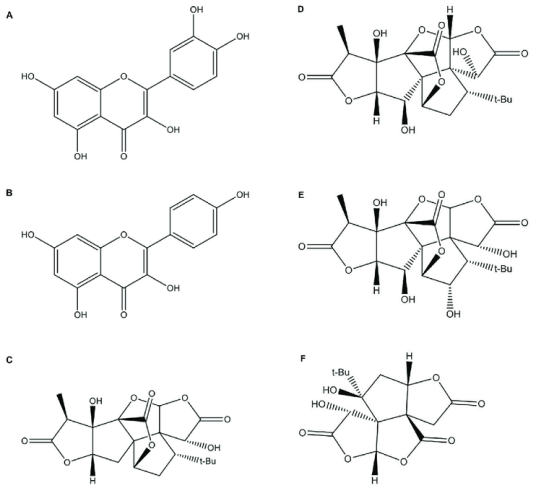

**Fig. 2.** Chemical structures of the Ginkgo biloba extract [GbE]: [A] quercetin; [B] kaempferol; [C] gingkolide A; [D] ginkgolide B; [E] ginkgolide C; [F] bilobalide [57]

*Ginkgo biloba* is one of the oldest plants in the world from the Ginkgoaceae family that has many pharmacological benefits [54]. This plant consists of two main active compounds: terpene trilactones and flavonoids [Figure 2]. The terpene trilactones, including ginkgolides and bilobalide, are assumed to be the main components most frequently used, especially in studies to determine their effect on the central nervous system and cardiovascular system since the flavonoids are considered difficult to penetrate the blood-brain barrier [55-58].

Ginkgolide, one of the major components in *Ginkgo biloba,* is known to have the potential to provide therapeutic effects in various diseases. A study by You et al. demonstrated that administration of ginkgolide A [GA] could improve cardiac function, reduce levels of cardiac oxidative stress markers, and enhance eNOS signaling in congestive heart failure [CHF] mice [59]. Other therapeutic benefits produced by the *Ginkgo biloba* plant include producing neuroprotective effects [60], increasing antioxidant enzymes, inhibiting NADPH-oxidase activity in various tissues [61, 62], and has the ability to inhibit DNA damage and initiate DNA repair in the hippocampus [63].

Erectile dysfunction [ED] is one of the complications caused by diabetes mellitus [DM]. Reactive oxygen species [ROS] have a role in the development of erectile dysfunction in men with DM. Several studies reported an increase in NOX2 as a marker of oxidative stress in the penis of a type 2 DM rat model [64, 65]. Wang et al. conducted a study by giving ginkgolide B 5 mg/kg/BW in diabetic rats. The results of the study showed a decrease in NOX2 and NOX4 protein expression [66]. This shows the potential of ginkgo biloba to overcome erectile problems through the antioxidant effect produced by the ginkgolide compound in it.

### 6.3 *Epimedium*

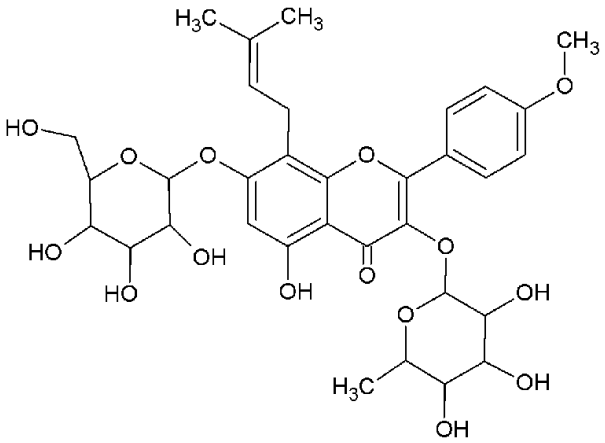

**Fig. 3.** Chemical structure of icariin [72]

*Epimedium, or* horny goat weed, has been used in traditional Chinese medicine for a long time. Epimedium belongs to the Berberidaceae family and genus *Epimedium* L. Various health problems that are overcome by giving *Epimedii herba* [EH] include impotence, female infertility, dysuria, rheumatic arthritis, geriatric depression, and angina pectoris [67, 68]. *Epimedium* is the dried leaves of the medicinal plant *Epimedium* L with flavonoids as the chemical basis [69]. *E. koreanum* Nakai, as one of the species, reported being able to regulate sexual behavior in both in vivo and in vitro studies [70, 71]. Icariin [Figure3] is one of the major bioactive compounds found in Epimedium and is used as a chemical marker for EH [69, 72]. Previous studies have shown that icariin has a protective effect on atherosclerosis through several cellular mechanisms, such as endothelial dysfunction, macrophage-derived foam cell formation, aberrant proliferation and migration of smooth muscle cells, and platelet activation [73].

Studies in mice have shown that penile erection involves activating signaling pathways cascades in the process of angiogenesis, cell survival and proliferation, and anti-fibrosis. Kwon et al. conducted research using the cavernous nerve's electrical stimulation to induce penile erection. Stimulation of the cavernous nerve can increase the expression of factors involved in angiogenesis, cell survival signaling pathways, and intracellular proliferation but decreases signaling activity in tissue fibrosis [74].

Chung et al. investigated the molecular effects and signaling pathways of icariin on angiogenesis using Human umbilical vein endothelial cells [HUVECs]. The results of this study indicate that the administration of icariin can increase the phosphorylation of ERK and Akt in a dose-dependent manner using Western blot analysis [75]. ERK and Akt's phosphorylation is a signaling mechanism that has a critical role in the angiogenesis process [76, 77].

Activation of endothelial nitric oxide synthase [eNOS] will produce nitric oxide [NO], which has a critical role in the angiogenesis process [78]. Based on this, Chung et al. observed the effect of icariin on NO and eNOS regulatory processes in HUVECs. The results showed that the phosphorylation of eNOS increased after icariin administration in a dose- and time-dependent manner. Examination of NO levels showed a significant increase compared to the control group [75]. Based on these studies, it is possible that icariin may also exert an effect on angiogenic signaling pathways in the corpus cavernosum endothelial cells.

Shindel et al. conducted a study on rats by giving icariin doses of 1 mg/kg, 5 mg/kg, and 10 mg/kg. The examination was carried out by observation at the parameters of nNOS, eNOS, and calponin as a regulatory protein associated with actin filament activity in the smooth muscle of penile tissue. Immunohistochemical examination showed that nNOS and eNOS positivity was higher in the icariin group compared to the control group. In the calponin staining test, there was a high intensity in the icariin 1 mg/kg group. These results were supported by Western blot analysis, which showed that penile tissue containing calponin was significantly higher in the icariin group than in the control group [79, 80].

### 6.4 Black pepper

Black pepper [*Piper nigrum* L] belongs to the Piperaceae family, and the genus *Piper* is one of the spices that is widely used in the food production process. There are various components of secondary metabolites in black pepper, including alkaloids, glycosides, terpenoids, steroids, flavonoids, tannins, and anthraquinones [81].

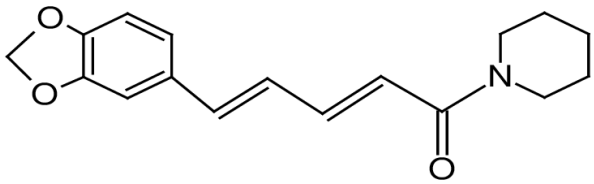

**Fig. 4.** Chemical structure of Piperine [84]

Piperine [Figure 4], one of the major alkaloid components in black pepper, has been widely studied for its use in traditional medicine [82-84].

Various utilization of piperine in health includes an anti-diabetic agent that can increase insulin and leptin sensitivity and reduce body weight in obese rat models [85]. Piperine is also known to have anti-inflammatory effects [86], anti-cancer activity [87], and antimicrobial potential [88].

A previous study by Septiyorini et al. observed the erectile ability in rats by giving black pepper extract in doses of 3.33 mg/kg BW, 6.66 mg/kg BW, and 13.32 mg/kg BW. Erectile ability was observed for eight weeks by measuring the total penile reflex [TPR], which was calculated by adding up the frequency of erection, quick flip, and long flip. The results showed increased TPR from the 1st to the 5th week of observation in rats given black pepper extract [89]. The benefits of the piperine compound in increasing penile erection ability are supported by other studies which state that piperine has the potential as an antioxidant that can protect nitric oxide from free radicals and can increase eNOS activity [90].

The increase in TNF-α as a marker of cell inflammation will induce ROS formation, which can lead to erectile problems. Several studies have reported that various Piper species have an inhibitory effect on TNF-α in endothelial cells [91]. Cell adhesion molecules have a major role in recruiting and migrating the inflammatory cells to the location of the inflammation. Piperine exhibited an inhibitory action on nuclear factor-ϰB [NF-ϰB], resulting in decreased expression of TNF-induced cell adhesion molecules in endothelial monolayer [92].

### 6.5 *Tribulus terestris*

*Tribulus terestris* [TT] is a plant that belongs to the Zygophyllaceae family and the genus *Tribulus*. The steroidal saponin component is thought to have a critical role in the biological activity of the products derived from this plant [93]. Research on the pharmacological action of TT has been carried out, including anti-diabetic agents [94], as a treatment for cardiovascular disease [95], exert a protective effect on neuronal cells [96], and showed an antitumor activity [97].

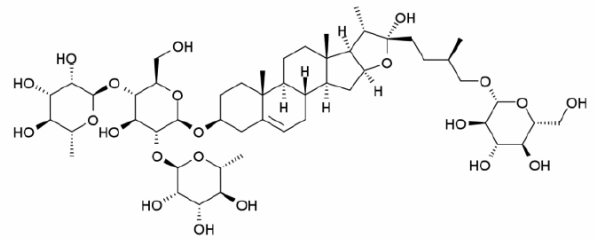

**Fig. 5.** Chemical structure of protodioscin [100]

Researchers have identified several components in the TT extract, especially steroidal saponins, flavonoids, tannins, terpenoids, polyphenol carboxylic acids, and alkaloids [98]. Protodioscin [Figure 5], as the main active component of steroidal saponins, is thought to have a critical role in the pharmacological process of TT [99, 100].

Several studies on the potential of TT in erection problems have also been carried out. The study by Kam et al. showed that the administration of TT produced a relaxant effect in a concentration-dependent manner on the rabbit corpus cavernosum, and there was a significant increase in cAMP. This suggests TT's potential mechanism of action in the erection process via the NOS pathway [101]. Do et al. conducted a similar study using TT extract in a dose of 0.5 mg; at 1, 2, and 4 mg. The study showed an increase in cAMP in the rabbit corpus cavernosum. Observations revealed that administration of TT extract at doses of 0.5 and 4 mg resulted in lower cAMP concentrations than doses of 1 and 2 mg. This indicates that there is no concentration-dependent pattern in this result of the study [102].

A study by Zhang et al. showed a repairing effect of gross saponins of Tribulus terrestris [GSTT] on the endothelial function of type 2 diabetes mellitus [T2DMED] rat model. In the GSTT administration group, there was an increase in NO levels and a decrease in ROS in the rat penile tissue. Increased cGMP levels were also observed in the GSTT group compared to T2DMED. This study also revealed that GSTT downregulates ROS expression and reduces oxidative stress in the corpus cavernosum [103].

### 6.6 *Eurycoma longifolia*

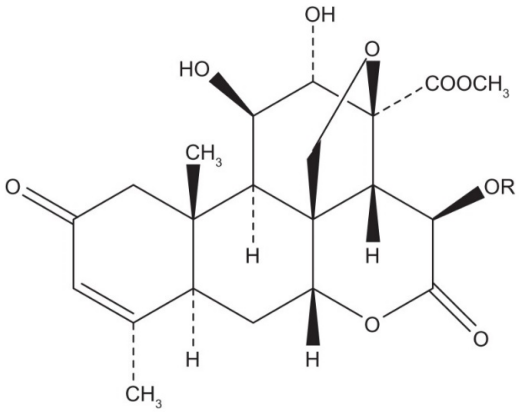

**Fig. 6.** Basic chemical structure of quassinoids [109]

*E. longifolia, commonly* called "Tongkat Ali" among Malaysians, belongs to the Simaroubaceae family and the genus *Eurycoma*. *E. longifolia* is a plant widely used in herbal medicine because it is believed to have an aphrodisiac and energy-boosting effect [104-107]. Quassinoids [Figure 6] are one of the components always found in plants from the Simaroubaceae family and are known to have various therapeutic effects for health, including anti-cancer, anti-malarial, and treatment of dysentery [104, 108].

RhoA and Rho-associated kinase [ROCK] are found in various tissues, including neural and endothelial tissue of corpora cavernosa. RhoA and ROCK have important roles in the regulation of multiple functions in the body, including the development of erectile problems [110]. A study by Ezzat et al. showed that administration of *E. longifolia* root extract showed more than 50% inhibitory activity against ROCK-II [107]. A previous study stated that administration of E. longifolia showed PDE5 inhibitory activity in the corpus cavernosum so that it could prevent cGMP breakdown and increase the duration of cGMP expression in smooth muscle tissue [111].

The penile erection process involves the important role of the RAS in regulating the balance of action of bradykinin [BK]-induced relaxation and angiotensin II [Ang II]-induced contraction in the corpus cavernosum [112]. A previous study stated that there was an induced relaxation effect in the corpus cavernosum of rats due to the administration of pure extracts of *E. longifolia* roots/ DCM-I root extract [113]. The molecular ability of pure extracts of *E. longifolia* roots/ DCM-I to downregulate the expression of Ang II-induced contractions and increase BK-mediated relaxations may be the underlying cause of the physiological processes of penile erection [114].

## 7 Conclusion

*Panax ginseng, Ginkgo biloba, Epimedium,* Black pepper, *Tribulus terestris*, and *Eurycoma longifolia* has the molecular potential to be involved in the physiological process of an erection. It has potential as a treatment for

erectile dysfunction. Further research to support the results of this literature review is needed through in-vitro and in-vivo experiments.

We are thankful to all those who offered technical help while writing this paper.

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