



## INTERACTION OF SILDENAFIL WITH HERBAL SUPPLEMENTS: A REVIEW

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Erectile dysfunction (ED) is defined as a man's inability to achieve or maintain an erection long enough to complete sexual activity. Sildenafil (SILD) is a drug that is used to treat ED all over the world. In this review article, the interactions between SILD and herbal supplements recorded in the literature were summarized using the Medline database (via PubMed) and the key-words: Sildenafil, herbal supplements, and interactions. In the present review article, pharmacokinetic (PK) and pharmacodynamic (PD) interactions were reported during co-administration of herbal supplements with SILD. Reduction in SILD bioavailability was found as a result of interaction of SILD with Horny goat weed, Thai ginseng, Arugula, Black seed, Garden cress, Fenugreek, and Pummelo juice in human and/or animal models. Meanwhile, Citrus lemon juice has not significantly altered the PK of SILD. Also, PD interactions were found as a result of the interaction of Curcumin, Yohimbine, and Pomegranate juice in human and rat models. Healthcare professionals should be aware of this potential and researchers should strive to fill the numerous gaps in our present understanding of this problem.

### INTRODUCTION

Erectile dysfunction is defined as the inability to achieve or maintain an erection long enough to complete sexual activity. It's a complicated condition that's brought on by both physical and psychological factors<sup>1&2</sup>. SILD is a medicine that is used to treat ED all over the world<sup>3</sup>.

SILD is an orally given Phosphodiesterase-5 (PDE-5) inhibitor that has been shown to be an effective treatment for male ED caused by organic malfunction, psychological causes, or a combination of causes. Furthermore, SILD has been shown to be very effective in clinical settings, with a broad margin of safety, patient satisfaction, and better quality of life in the majority of patients<sup>3-5</sup>.

SILD is rapidly absorbed after oral administration<sup>6</sup> and is mainly metabolized by the cytochrome P450 (CYP) hepatic isoenzymes 3A4 (a major pathway) and 2C9 (a minor route)<sup>7</sup>. CYP450 transforms SILD into an active form of N-desmethyl metabolite

which has been found to account for around half of SILD potency and activity. SILD and its metabolite are strongly bound to plasma proteins (96%) and have terminal half-lives of 4 hours<sup>8</sup>.

Despite the widespread use of herbal treatments, there are few reported herb-drug interactions, and many of those that have been detected are based on single case reports<sup>9</sup>. Because CYP3A4 plays a key role in the biotransformation of SILD, using medications or herbal treatments that inhibit or induct CYP3A4 at the same time can lead to harmful drug interactions<sup>10</sup>.

Herb-drug interactions may be more common than drug-drug interactions, owing to the fact that pharmaceuticals typically contain single chemical entities, but nearly all medicinal supplements (including single-herb formulations) contain combinations of pharmacologically active ingredients<sup>11</sup>. When a herbal supplement and a drug share a common absorption, distribution, metabolism, or excretion mechanism, the drug's concentration

at the site of action may be changed. Herb-drug interactions can also form the basis of pharmacodynamic mechanisms, which are characterized by direct pharmacologic activities of an herbal extract that are unrelated to changes in blood concentrations<sup>12</sup>.

Herbal remedies are thought to be safe by the general public because they are natural. This, however, is a dangerous oversimplification. Herbal side effects have been recorded in a variety of ways, including adverse events caused by drug-herb interactions<sup>13-15</sup>.

The purpose of this review article is to provide an overview of the clinical data on herbal supplements and SILD interactions. Herbal supplements and SILD interactions are reviewed, with concrete examples, mechanisms, and other clinical observations. To generate a comprehensive summary of reported interactions between herbal supplements and SILD, an intensive investigation of scientific literature in the PubMed database, Research Gate, Google Scholar, Science Direct, and recent conference papers was undertaken. Table 1 lists the clinical herbal supplements-SILD interactions that have been studied, as well as the level of evidence for each interaction. The overall purpose of this review article is to increase pharmacists' and physicians' understanding of this concern and thereby protect patients' health.

## MEDICINAL HERBS AND SILDENAFIL INTERACTIONS

### Horny goat weed

Horny goat weed (*Epimedium sagittatum*) is used widely to treat male ED. The principal functions of horny goat weed included the nutrition and reinforcement of the renal viscera, which resulted in the restoration of erectile function in males. The PK profile data in the literature is scarce, and is mostly focused on icariin, the predominant pure product from the horny goat weed species<sup>16-18</sup>.

A PK interaction study conducted in rats was designed to explore dose related interaction between the extract of horny goat weed (1/2 g/kg/day) for three consecutive days and intravenous injection with SILD (10/30 mg/kg) SILD. The study demonstrates that

there were significant herb-drug interaction between horny goat weed extract and SILD at low and high daily doses, suggesting that co-administration use of horny goat weed extract and SILD in clinical practice should be prevented due to possible herb-drug interactions<sup>19</sup>.

### Thai ginseng

*Thai ginseng* (*Kaempferia parviflora*) The medicinal plant *Thai ginseng*, or Krachaidum, belongs to the Zingiberaceae family. *Thai ginseng* has been demonstrated to have antiallergenic, anti-inflammatory, antimutagenic, anti-depressive, anticholinesterase, antimicrobial, anticancer, antiulcer, cardioprotective, anti-obesity, and aphrodisiac properties in a variety of pharmacological trials<sup>20</sup>.

In a PK study aimed to investigate the effect of *Thai ginseng* extract (250 mg/kg daily for 9 days) on the PKs of SILD in a random manner, rats were divided into several groups. The findings revealed a strong interaction between *Thai ginseng* extracts and SILD, resulting in a reduction in the area under the curve (AUC) and maximum concentration ( $C_{max}$ ) values of SILD respectively<sup>21</sup>. In order to avoid possible therapeutic failure in patients with ED, the interaction between *Thai ginseng* extract and SILD should be taken into account for clinical practice in order to prevent possible therapeutic failure in the treatment of sexual dysfunction.

### Green tea

*Green tea* (*Camellia sinensis*, Theaceae) has been studied for its health advantages in cancer prevention, cardiovascular disease prevention, anti-inflammatory, antibacterial, antiangiogenic, antioxidative, neuroprotective, and cholesterol-lowering activities<sup>22</sup>.

A PK study published by Hegazi 2013 investigated the effect of *green tea* on the PK profile of SILD in healthy males. *Green tea* and SILD co-administration increased the extent but not the rate of SILD absorption. It resulted in greater  $C_{max}$  and AUC, as well as a considerable drop in the elimination rate constant of SILD. Patients who use *green tea* may require lower SILD doses<sup>23</sup>.

**Table 1:** Herbal supplements-SILD interactions.

<b>Herb</b>	<b>Study type</b>	<b>Outcome measures</b>	<b>Effect on PK/PD of SLD</b>	<b>Mechanism of interaction</b>	<b>References</b>
Horny goat weed	Rats	PK	Reduction in the AUC	Induced CYP3A4 activity	Hsueh et al., 2013 (19)
Thai ginseng	Rats	PK	Reduction in the AUC and $C_{max}$	Induced CYP3A4 activity	Mekjaruskul and Sripanidkulchai 2015 (21)
Green tea	Human	PK	Increase in the $C_{max}$ and $AUC_{0-\infty}$ , decrease in the $k_e$ and prolonged $t_{1/2}$	Inhibited CYP3A4 activity	Hegazi, 2013 (23)
Arugula	Rats	PK	Reduction in the $C_{max}$ and AUC	Induced CYP3A4 activity	Mallah et al., 2017 (26)
Black seed	Dogs	PK	Reduction of the $C_{max}$ , $AUC_{0-\infty}$ and $t_{1/2}$	Induced CYP3A4 activity	Al-Mohizea et al., 2015 (31)
Garden cress	Dogs	PK	Reduction in the $C_{max}$ and AUC	Induced CYP3A4 activity	Al-Mohizea et al., 2015 (31)
Fenugreek	Dogs	PK	Reduction in the $C_{max}$ and AUC	Induced CYP3A4 activity	Al-Mohizea et al., 2015 (31)
Marijuana	Human	PK	Increase in the $C_{max}$ and AUC	Inhibited CYP3A4 activity	. Murtadha et al., 2021 (33)
Grapefruit juice	Human	PK	Increase in the $AUC_{0-\infty}$ with no change in the $C_{max}$ and delayed sildenafil absorption	Inhibited CYP3A4 activity	Jetter et al., 2002 (36)
Bitter orange juice	Human	PK	Increase in the $AUC_{0-\infty}$ , no change in $t_{max}$ , no change in $t_{1/2}$ and reduction in the apparent oral clearance	Inhibited CYP3A4 activity	Abdelkawy et al., 2016 (10)
Citrus lemon juice	Human	PK	No significant alterations in the PK of sildenafil.	Inhibited CYP3A4 activity	Abdelkawy et al., 2016 (10)
Pummelo juice	Human	PK	Reduction in the $C_{max}$ and $AUC_{0-\infty}$	Induced CYP3A4 activity	Al-Ghazawi et al., 2010 (43)
Curcumin	Rats	PD	Improve in nerve functions, biochemical, and histopathological parameters	Inhibition of mitogen protein kinase and inhibition of COX-2 pathways	Kaur et al., 2017 (48)
Yohimbine	Rats	PD	A dose-dependent relaxing effect on rat corpus cavernosum strips and an increase in nitric oxide level in rats' penis	Alpha-2-adrenoceptor antagonist may increased penile blood flow	Saad et al., 2013 (50)
Pomegranate juice	Human	PD	Low-flow priapism	Antioxidant effect might enhanced the bioavailability of endothelial nitric oxide levels	Senthilkumaran et al., 2012 (52)

## Arugula

*Arugula* (*Eruca sativa*) The annual herbaceous plant *Arugula*, sometimes known as rocket plant (jarjeer), belongs to the Brassicaceae family. *Arugula* is a garden plant that has been used in traditional medicine to increase male sexual desire<sup>24-26</sup>.

In a crossover experiment with a washout period of two weeks conducted on rats, the  $C_{max}$  of SILD was increased after *Arugula* was pre-administered. Moreover, when SILD was pre-administered to a group of rats with *Arugula*, the AUC of SILD increased considerably. The results imply that co-administering of *Arugula* with SILD improves its PK profile in rat plasma. In the presence of *Arugula*, the concentration of SILD in rat plasma increased substantially. In conclusion, when sexual stimulants were combined with SILD, some care had to be taken<sup>26</sup>.

## Black seed, Garden cress, Fenugreek

*Black seed* (*Nigella sativa*) is used to cure and prevent a variety of ailments and conditions, particularly asthma, diarrhea, and dyslipidemia<sup>27</sup>. *Black seed* has anti-inflammatory, analgesic, anti-diabetic, anti-hyperlipidemic, anti-convulsant, anti-microbial, anti-ulcer, anti-hypertensive, anti-asthmatic, and anti-cancer effects, according to laboratory studies. Antioxidant, immunomodulating, cytoprotective, and an inhibitory effect on certain inflammatory mediators are some of the ways in which it works<sup>28</sup>.

*Garden cress* (*Lepidium sativum*) is used for different conditions, such as cough, vitamin C deficiency, constipation, poor immunity, and as a diuretic. It is useful as a poultice for sprains and for leprosy, skin diseases, dysentery and diarrhea<sup>29</sup>.

*Fenugreek* (*Trigonella foenum-graecum*) is an annual crop from the Fabaceae family. Simple alkaloids such as trigonelline, choline, gentianine, carpaine, and saponine are the most prominent ingredients. Fenugreek has been shown to have anti-diabetic, anti-cancer, antibacterial, anti-parasitic, and cholesterol lowering properties<sup>30</sup>.

Al-Mohizea and partners investigated the effects of *Black seed*, *Garden cress* and *Fenugreek* (pretreated for one week) on the PK

of orally administered SILD using beagle dogs (100 mg for each).

*Black seed* reduced the AUC,  $C_{max}$ , and half-life  $t_{1/2}$  of SILD, whereas *Garden cress* and *Fenugreek* decreased the  $C_{max}$  and AUC of SILD dramatically after co-administration. Furthermore, it was observed that taking any of the explored herbs with SILD at the same time had an effect on its PKs. The use of researched herbs in combination should be done with caution, since it may lower SILD bioavailability<sup>31</sup>.

## Marijuana

*Marijuana* (*Cannabis*) has been used for the relief of pain and seizures. It contains more than 100 natural compounds that have been identified as phytocannabinoids<sup>32</sup>. In a human study, healthy participants were randomly assigned to one of three groups: nonsmokers, cigarette smokers, and *Marijuana* users. In the cigarette smokers' group, the  $AUC_{0-t}$  of SILD (50 mg) revealed a statistically significant increase, whereas in the non-smokers group, there was a non-significant increase. Furthermore, among cigarette smokers and *Marijuana* users, the  $C_{max}$  of SILD also increased respectively<sup>33</sup>. Cigarette smoking significantly enhances SILD exposure while having no influence on its pharmacodynamics, safety, or tolerance.

## Grapefruit juice

*Grapefruit juice* (*Citrus paradisi* Macfad) inhibits the P-glycoprotein (P-gp) pump and changes the PKs of several drugs by blocking various enzyme systems, resulting in enhanced bioavailability<sup>34&35</sup>. The bioavailability of SILD was increased in a randomized crossover study in which male volunteers received a single 50 mg dose of SILD when co-administered with *Grapefruit juice*. Although patients are unlikely to be harmed if they take *Grapefruit juice* at the same time, it is prudent to avoid this combination<sup>36</sup>.

## Bitter orange and Citrus lemon

Citrus fruits and drinks are widely consumed around the world due to their purported health benefits, primarily anti-oxidative and anti-proliferative properties. Fruit juice-drug interactions have received a lot of attention in clinical practice. *Bitter orange*

*juice* (Seville orange), one of the common varieties of the *Citrus aurantium* species. *Bitter orange juice* has been utilized as an ingredient in dietary supplements and promoted as a weight loss aid<sup>37-39</sup>.

An open-label, crossover study in nine healthy male healthy male volunteers found that *Bitter orange juice* increased the AUC<sub>0-</sub> and C<sub>max</sub> of SILD by 44% and 18% respectively without affecting the time to reach peak plasma concentration t<sub>max</sub>. Also, *Bitter orange juice* significantly reduced the clearance of SILD by 30% without affecting t<sub>1/2</sub>. In the contrast, *Citrus lemon juice* (lemon juice) did not cause any significant changes in the PKs of SILD. The enhancement of SILD bioavailability by *Bitter orange juice* may be related to the inhibition of intestinal CYP3A4 and/or P-gp. On the other hand, *Citrus lemon juice* had no effect on the PK profile of SILD<sup>10</sup>. Further investigations are necessary to confirm the obtained results.

### Pummelo juice

*Pummelo* (*Citrus grandis*) is an exotic large citrus fruit that is an ancestor of the common grapefruit. It was found that *Pummelo* has different PK interactions when co-administered with specific medications. However, *Pummelo* was shown to augment the bioavailability of tacrolimus, cyclosporine, and felodipine felodipine<sup>40-42</sup>. In a randomized, two-period, two-treatment, two-sequence, single dose, crossover clinical study, the impact of *Pummelo* juice on the PKs of SILD (equivalent to 50mg) in healthy male participants in fasting conditions was investigated and compared to water as a control. The study results showed that *Pummelo* juice led to a reduction in the bioavailability by 60% of SILD So, patients should avoid consuming *Pummelo* juice before or after administering SILD<sup>43</sup>.

### Curcumin

*Curcumin* (*Curcuma longa*) is one of the most well studied functional foods. *Curcuma longa* and *Curcuma domestica*, both Zingiberaceae members, are widely cultivated in Asia's tropical regions<sup>44&45</sup>. *Curcumin* has anti-inflammatory, anti-mutagenic, antibacterial, and anticancer properties. Neuropathic pain associated with chronic alcohol intake is a bothersome problem that

affects both the central and peripheral nerve systems and has no satisfactory treatment to date<sup>46&47</sup>. In a study on alcohol-induced neuropathic pain in rats, the combination of *Curcumin* and SILD was found to have a protective effect. *Curcumin* and SILD co-administered by the intraperitoneal route (i.p.) of administration were found to increase nerve function considerably. As a result, it is postulated that employing *Curcumin* and SILD together could add a new dimension to the treatment of alcohol-induced neuropathic pain that affects both the central and peripheral nerve systems<sup>48</sup>.

### Yohimbine

*Yohimbine* (*Pausinystalia johimbe*) is the major alkaloid found in the stem bark of yohimbe, *Pausinystalia johimbe* (Rubiaceae). In rats, the effects of *Yohimbine hydrochloride* (0.2 mg/kg, i.p.) and sildenafil citrate (20 mg/kg, i.p) on cold stress-induced ED were investigated. *Yohimbine* and SILD were given to rats for 14 days consecutively, 1 hour before the stress session, to see if they had any effect. The results demonstrated that both *Yohimbine* and SILD have a dose-dependent vasorelaxant action on rat corpus cavernosum strips, which is supported by SILD's rise in nitric oxide levels in rats' penis<sup>49&50</sup>.

### Pomegranate juice

Fruit juice-drug interaction has received wide attention with numerous scientific and clinical investigations<sup>51</sup>. One report found a link between *pomegranate juice* (*Punica granatum*) and SILD and the development of low-flow priapism, an emergency case that necessitates rapid medical intervention to avoid complications and the danger of impotence. Researchers also suggested that patients taking SILD should be aware of this potential interaction and cautioned against concurrent use in the future. In the meantime, the manufacturers should be asked to include this in the patient information leaflet. Also, clinicians and practitioners should be aware of this interaction while treating and prescribing SILD<sup>52</sup>.

## CONCLUSION

Herbal supplements can interact with prescription drugs, which may lead to major clinical repercussions. In these kinds of interactions, both PK and/or PD mechanisms have been proposed to play an important role. Although the underlying mechanisms for the altered drug effects and/or concentrations of concomitant herbal medicines are yet to be determined. Despite the highly use of herbal remedies, there are few documented herb-drug interactions.

Based on a PKs perspective, SILD bioavailability was found to be altered by induction and or inhibition of CYP3A4 in conducted PK interaction studies between the mentioned herbal supplements and SILD in human and/or animal models. Furthermore, PD interactions were found as a result of the interaction of Curcumin, Yohimbine, and Pomegranate juice in human and rat models as shown in table 1.

Herb-drug interactions may be beneficial by enhancing the efficacy and reducing the toxicities of the co-administered drugs. However, herb-drug interactions may increase toxicity or even be fatal. Thus, more studies are needed to confirm and assess the clinical significance of these potential herb-drug interactions. Herb-drug interactions are a reality and can present a serious threat to human health. Healthcare professionals should be aware of this potential and researchers should strive to fill the numerous gaps in our present understanding of this problem.

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## نشرة العلوم الصيدلية جامعة أسيوط



### تفاعل السيلدينافيل مع المكمّلات العشبية: مراجعة

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قسم الصيدلانيات والصيدلة الصناعية ، كلية الصيدلة ، جامعة الأزهر ، غزة ، فلسطين صندوق بريد ١٢٧٧

يُعرَّف ضعف الانتصاب بعدم قدرة الرجل على تحقيق الانتصاب أو الحفاظ عليه لفترة كافية لإكمال النشاط الجنسي. السيلدينافيل هو دواء يستخدم لعلاج الضعف الجنسي في جميع أنحاء العالم. في هذه الورقة البحثية، تم تلخيص التفاعلات بين السيلدينافيل والمكمّلات العشبية المسجلة المنشورة في مجالات عالمية باستخدام قاعدة بيانات PubMed (عبر PubMed) والكلمات الرئيسية: السيلدينافيل والمكمّلات العشبية والتفاعلات ولجمع البيانات الموجودة في البحث ، تم التحقيق في المراجع في الأدباء التي تم تحليلها. علاوة على ذلك ، في المراجعة الحالية ، تم الإبلاغ عن تفاعلات حركية وдинاميكية الدواء أثناء الإدراة المشتركة للمكمّلات العشبية مع السيلدينافيل. تم العثور على انخفاض في التوافر الحيوي للسيلدينافيل نتيجة تفاعل السيلدينافيل مع Kaempferia و Epimedium sagittatum و Trigonella foenum-graecum و Lepidium sativum و Nigella sativa و parviflora و Eruca sativa و Trigonella foenum-graecum و Pummelo في النماذج البشرية و / أو الحيوانية. في هذه الأثناء ، لم يغير عصير الليمون بشكل ملحوظ المعاملات الحركية للسيلدينافيل. اضافة الى ذلك ، تم العثور على تفاعلات ديناميكية نتيجة تفاعل عصير الكركمين ، يوهمبين ، وعصير الرمان مع السيلدينافيل في نماذج الإنسان والجرذان. يجب أن يكون المتخصصون في الرعاية الصحية على دراية بهذه الإمكانيات ويجب على الباحثين السعي لسد الفجوات العديدة في فهمنا الحالي لهذه المشكلة والعمل على تجنبها.