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REVIEW ARTICLE

A literature perspective on the pharmacological applications of yohimbine

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ABSTRACT

Introduction: Phytochemicals have garnered much attention because they are useful in managing several human diseases. Yohimbine is one such phytochemical with significant pharmacological potential and could be exploited for research by medicinal chemists. It is an indole alkaloid obtained from various natural/synthetic sources.

Aims and Results: The research on yohimbine started early, and its use as a stimulant and aphrodisiac by humans has been reported for a long time. The pharmacological activity of yohimbine is mediated by the combined action of the central and peripheral nervous systems. It selectively blocks the pre and postsynaptic α_2-adrenergic receptors and has a moderate affinity for α1 and α2 subtypes. Yohimbine also binds to other behaviourally relevant monoaminergic receptors in the following order: α-2 NE $>$ 5HT-1A$>$, 5HT-1B $>$ 1-D $>$ D3 $>$ D2 receptors.

Conclusion: The current review highlights some significant findings that contribute to developing yohimbine-based drugs. It also highlights the therapeutic potential of yohimbine against selected human diseases. However, further research is recommended on the pharmacokinetics, molecular mechanisms, and drug safety requirements using well-designed randomized clinical trials to produce yohimbine as a pharmaceutical agent for human use.

KEY MESSAGES

- Yohimbine is a natural indole alkaloid with significant pharmacological potential.
- Humans have used it as a stimulant and aphrodisiac from a relatively early time.
- It blocks the pre- and postsynaptic α2-adrenergic receptors that could be exploited for managing erectile dysfunction, myocardial dysfunction, inflammatory disorders, and cancer.
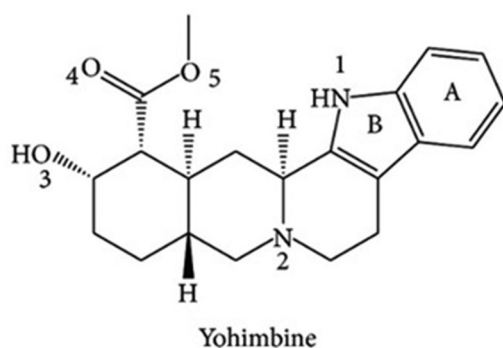
Introduction

Yohimbine is a monoterpenoid, indole alkaloid with potent pharmacological effects obtained from several biological sources [1]. It is also called quebrachine, aphrodine, corynine, and hydroaerogotocin. Indole-based pharmaceutical agents constitute a significant class of therapeutic molecules, and much progress has been made in their utilization in current therapies [2–4]. Yohimbine has been used as a stimulant and aphrodisiac to improve erectile function [5]. Yohimbine is a prototypical α2-receptor antagonist licenced in Germany (since 1978) and Canada (since 1951) as therapy for erectile dysfunction [6]. Over several decades, it has been used as a therapeutic agent for sexual difficulties and is a comparatively safer agent with few known adverse effects [7]. The hyperadrenergic effects of yohimbine are beneficial in various disease conditions such as erectile dysfunction, myocardial dysfunction, inflammatory disorders, and cancer [8–11]. It also has antidiuretic, anti-adrenaline, mydriatic, serotonin antagonist properties [5]. Yohimbine combines effects of central and peripheral nervous system, including blocking of pre- and postsynaptic α_2-adrenergic receptors [12]. The usual recommended

Figure 1. Molecular structure of yohimbine.

dose of pure yohimbine is 5–10 mg thrice a day. The side effects of α-2 adrenergic inhibition are often minor and short-lived. They consist of hypertension, perspiration, chest pain, sleeplessness, anxiety, and palpitations [10]. Despite extensive pharmacological data, the exact mechanism of action of yohimbine is unclear and needs further research.

Chemistry of yohimbine

Yohimbine is a nitrogenous organic compound with the chemical formula $C_{21}H_{26}N_2O_3$ and a molecular weight of 354.44 g/mol (Figure 1). It is a 17, α-hydrox-yyohimban-16, α-carboxylic acid methyl ester. Tryptophan and the secoiridoid monoterpene secolo-ganin are the sources of this pentacyclic monoterpe-noid indole alkaloid [13,14]. Indole is a weak base comprising a pyrrole ring fused to a benzene nucleus and ten π-electrons moving throughout the structure [15]. Natural indole alkaloids have shown high thera-peutic potential in preclinical and clinical studies [4,15,16]. Several yohimbine stereoisomers have been identified based on their stoichiometric arrangement. The alkaloids are divided into four subfamilies based on the stereochemical arrangement around the D-ring: normal, allo, pseudo, and epiallo. The representative examples of these subfamilies are yohimbine, rauwols-cine, pseudoyohimbine, and reserpine [14]. Yohimbine synthesis is complicated because of the complex gen-eration of the pentacyclic rings containing five chiral centres [17]. It is colourless, weakly basic with a pK_a value of 6–7.5, highly soluble in alcohol, and sparingly soluble in water [18]. It is readily soluble in chloroform and ethanol and is sparingly soluble in diethyl ether. It has a melting point of 234 °C and decomposes at 302 °C [19]. Yohimbine hydrochloride undergoes vari-ous reactions like acidic and alkaline hydrolysis and photo-degradation [13]. The yohimbine reaction is resistant to acid catalysis and is remarkably stable at very low pH, probably due to the intramolecular H-

bonding between the β-hydroxyl group and the ester's acyl group. Awad et al. [20] studied the kinetics of yohimbine hydrolysis and reported its high stability. Hydrolysis is the main route of degradation of yohim-bine hydrochloride at pH 6 and 7 to form yohimbine acid, and it follows first-order kinetics. Around neutral pH, yohimbine hydrochloride is stable enough to develop a transdermal preparation. The yohimbine compounds meet fundamental drug-like criteria with DPQ and quantitative estimates of drug-likeness >0.5 [21].

## Isolation of yohimbine using different analytical approaches

Yohimbine hydrochloride (CAS: 146-48-5) was isolated for the first time from the bark of the *Pausinystalia yohimbe* tree in West Africa [22]. Humans have trad-itionally used this plant as a stimulant and aphrodisiac, particularly as herbal remedy to help erectile dysfunc-tion. Yohimbine has been also detected in *Alchornea floribunda* Müll. Arg., *Rauvolfia vomitoria*, *Rauwolfia nitida*, *Rauwolfia serpentina*, *Rauvolfia yunnanensis*, and other plants [5,23]. A summary of extracted yohimbine from different natural sources is listed in Table 1.

Synthesis of yohimbine

Several researchers synthesized yohimbine using mainly two general strategies. The first strategy involves creating a DE-ring system and then building a C-ring. On the other hand, building an ABC-ring and annulling a DE-ring are necessary for the second strat-egy [33]. The synthesis of a racemic mixture of yohim-bine was first achieved by a series of steps for constructing a DE trans group of naturally occurring pentacyclic indole derivatives [34]. Aimi et al. [35] syn-thesized yohimbine by converting some natural oxin-doles (pteropodine, isopteropodine, and isorhynchophylline) into corresponding indole alka-loids. Similarly, asymmetric synthesis of yohimbine was achieved by a series of reactions that included the asymmetric intramolecular Michael reaction [36]. Mergott et al. [37] and Herlé et al. [38] reported the catalytic asymmetric total synthesis of (+)-yohimbine using highly enantioselective thiourea-catalyzed acyl-Pictet–Spengler reaction and substrate-controlled intramolecular Diels–Alder reaction [37,38]. The asym-metric synthesis of (+)-yohimbine by Mergott et al. [37] was achieved in 11 steps with a 14% overall yield. On the other hand, the total synthesis of enantiopure

Table 1. Extraction of yohimbine from various natural sources.

Natural source	Plant part	Method of isolation	% yield	References
Pausinystalia yohimbe	Stem bark	HPTLC	0.56 mg/g	[24]
Pausinystalia yohimbe	Stem bark	Differential pulse voltammetry	2.3 µmol/L	[25]
Pausinystalia yohimbe	Stem bark	Non-aqueous capillary electrophoresis	1.17 mg/100 mg	[26]
Rauvolfia serpentina	Stem bark	Differential pulse voltammetry	2.9 µmol/L	[25]
Rauvolfia serpentina	Leaf	HPLC	0.537 mg/g	[27]
Rauvolfia serpentina	Root	HPLC	0.584 mg/g	[27]
Rauvolfia verticillata	Root	Ultrasonic-assisted extraction	3.841 mg/g	[28]
Rauwolfia serpentina	Whole plant	Column chromatography	2.1 mg/g	[29]
Rauvolfia tetraphylla	Leaves	HPLC	6.11%	[30]
Tribulus terrestris	Whole plant	UHPLC–MS/MS	62.74 pg/mg	[31]
Nicotiana tabacum	Stem	UHPLC–MS/MS	20.28 pg/mg	[31]
Peganum harmala	Seed	UHPLC–MS/MS	7.25 pg/mg	[31]
Rauvolfia verticillata	Root	pH-zone-refining counter-current chromatography	7.0 mg/g	[32]
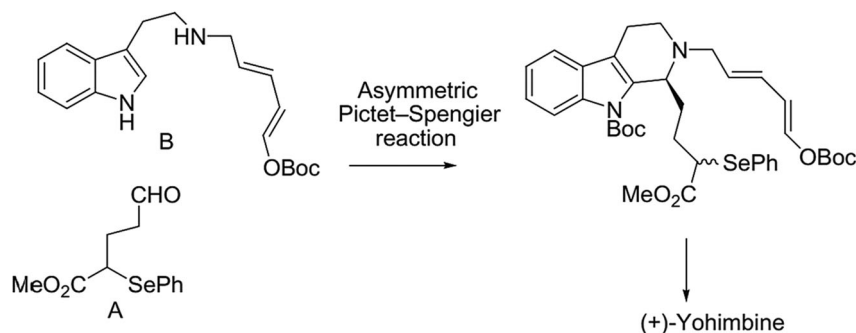
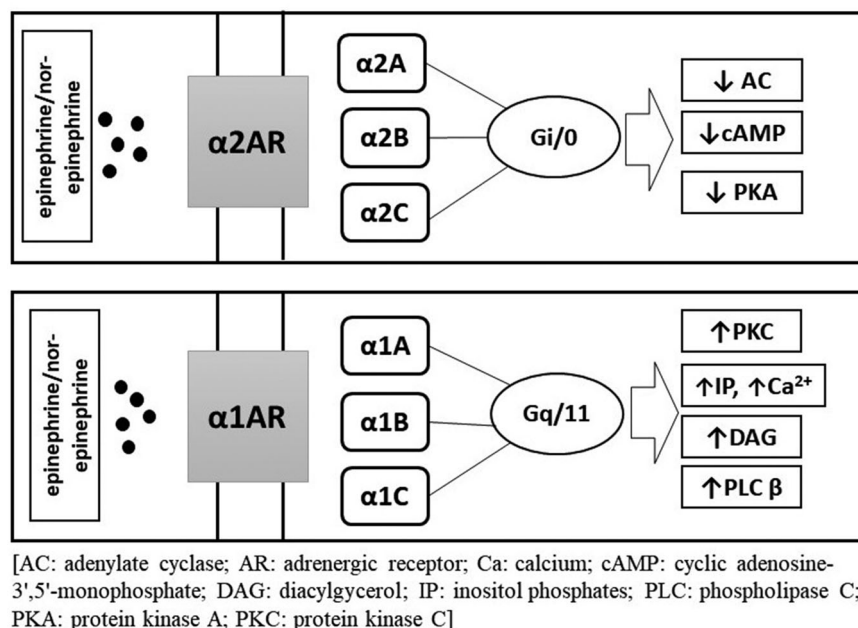**Figure 2.** Synthesis mechanism of yohimbine proposed by Herlé et al. [38].

(+)-yohimbine by Herlé et al. [38] involved 9 steps with an overall yield of 16% (Figure 2).

Similarly, Feng et al. [17] reported a bicyclic guanidine-catalyzed asymmetric tandem isomerization intramolecular-Diels–Alder reaction for the enantioselective catalytic synthesis of (+)-alpha-yohimbine with yield % in the range of 72–91%. Recently, Miller et al. [14] proposed a concise enantioselective approach for synthesizing yohimbine alkaloids with upto 65% yield. This method provides a powerful strategy for producing various complex alkaloids and related structures for biomedical applications [14].

Spectroscopic characterization of yohimbine

Yohimbine contains a pentacyclic ring structure with five chiral carbon atoms (C3, C15, C16, C17, and C20) and two nitrogen atoms [18]. Multiple chiral centres form several diastereomers, which can be separated under chromatographic conditions [39]. The two stereoisomers of yohimbine, rauwolscine, and corynanthine, differ little in terms of their physical characteristics and how they affect dopamine/serotonin receptors. In addition, yohimbine and reserpine share a similar structural makeup, even with different stereochemistry [40]. Benoin et al. [41] reported UV absorption spectrum of yohimbine in ethanol at a different excitation wavelengths of 286, 278, and 226 nm.

Similarly, the UV spectrum of yohimbine in methanol and H_2SO_4 exhibited three band maxima at 289, 282, and 225 nm [42]. In one study, Farouk et al. [13] reported a characteristic λ_{max} of yohimbine hydrochloride at 279–282 nm in the UV region. On the other hand, Joshi et al. [43] observed the UV spectrum of yohimbine hydrochloride in ethanol solution with band peaks at 289, 280, and 228 nm. The main transitions observed in the UV region are $\pi \to \pi^*$ and $n \to \pi^*$. A single band of low intensity in the range of 250–300 nm, with no significant absorption at shorter wavelengths, also suggests the $n \to \pi^*$ transition, which occurs at approximately 228 nm and is caused by the carbonyl group. The experimental analysis of yohimbine hydrochloride by Joshi et al. [43] revealed details about yohimbine molecular structure and biological activities. They reported 54 atoms in the yohimbine hydrochloride molecule, which gives 156 normal modes of vibrations, belonging to an irreducible representation of both Raman and IR active. The equilibrium geometries and harmonic vibrational wavenumbers of all 156 normal molecule modes reveal detailed information about the size, shape, charge density distribution, and structure–activity relationship by mapping electron density iso-surface with electrostatic potential. The CH stretching of the yohimbine ring showed a peak at 3057 and 3031 cm^{-1} in the Raman and 3087 and 3066 cm^{-1} in the IR

[AC: adenylate cyclase; AR: adrenergic receptor; Ca: calcium; cAMP: cyclic adenosine-3',5'-monophosphate; DAG: diacylgycerol; IP: inositol phosphates; PLC: phospholipase C; PKA: protein kinase A; PKC: protein kinase C]

Figure 3. Proposed signalling mechanism of adrenergic receptor family.

spectrum. On the other hand, the CC stretching vibrations of the ring are observed at 1636, 1571, and 1499 cm^{-1} in the Raman and 1624, 1572, and 1496 cm^{-1} in the IR spectrum. The N5H stretching vibration of the second ring showed an intense high peak at 3514 cm^{-1} in the IR spectrum. On the other hand, the CC stretching of this ring is reported at 1593 cm^{-1} in the Raman spectrum, having a very high intensity. Similarly, the NC stretching motions are reported high-intensity Raman spectrum at 1295 cm^{-1} and low-intensity IR spectrum at 1296 cm^{-1}. Six possible stretching vibrations, namely symmetric, asymmetric stretch, deformation modes, rocking modes, wagging modes, and twisting modes, are observed in $C_{18}H_2$ of the third ring. At 2895 cm^{-1} in the infra-red spectrum and 2945 cm^{-1} in the Raman spectrum, the symmetric stretching vibration of $C_{18}H_2$ is observed. While $C_{18}H_2$ exhibits wagging motions at 1381 cm^{-1} in the Raman spectrum and at 1385 cm^{-1} in the IR spectrum, deformation motions of $C_{18}H_2$ are observed at 1453 cm^{-1} in the Raman spectrum and 1454 cm^{-1} in the IR spectrum. In the Raman and IR spectra, the twisting mode of $C_{18}H_2$ is recorded at 1223 and 1221 cm^{-1} peaks, respectively. In the Raman spectra, $C_{18}H_2$ is found to be rocking at 894 cm^{-1}. A weak asymmetric mode of $C_{11}H_2$ is observed by CH_2 and CH vibrations of the fourth ring, with peaks at 2965 and 2960 cm^{-1} in the Raman and 2960 cm^{-1} in IR spectrum, whereas the symmetric vibration mode reported peaks at 2911 cm^{-1} in the Raman spectrum. Deformation modes of $C_{11}H_2$ are reported at

1478 cm^{-1} with high intensity in the Raman spectra and Twisting modes peaks at 1253/1208 cm^{-1} in the Raman and 1246/1207 cm^{-1} in the IR spectrum. In the Raman and IR spectra, the combined vibrations of the C_7H and C_6H stretching modes are observed at 2876/2894 cm^{-1} and 2883/2887 cm^{-1}, respectively. Due to the presence of two functional groups, a CH_3 and a hydroxyl group, that are joined by a carboxylic group, the fifth ring is assigned with a variety of vibrational modes. It has been observed that the weak band in the IR spectrum at 3670 cm^{-1} corresponds to the characteristic peak related to the stretching mode of the O1H group. The peaks at 1007 cm^{-1} in the Raman spectra and 1018/873 cm^{-1} in the IR spectrum are where the O1C13 stretching wavenumbers are found. There are many associated modes with the CH_3 group in this ring, including symmetric and asymmetric stretches, bends, rocks, and torsional modes. The asymmetric CH_3 group stretches are reported to have significant Raman intensity at 2989 cm^{-1} and weak IR intensity at 3024 cm^{-1}. In the IR spectrum, the CH_3 symmetric stretches are observed at 2935 cm^{-1} with a medium intensity. In the 1700–1800 cm^{-1} range, most the carboxylic group's distinctive characteristics are typically observed. The peak at 1754 cm^{-1} with weak intensity in the Raman and strong intensity at 1718 cm^{-1} in the IR spectra are both well matched to the high contributions of the C O stretching band, which are calculated to be at 1749 cm^{-1}.

Yohimbine's mass spectroscopic properties revealed fragment ions at m/z 323.1560 caused by CH_3OH
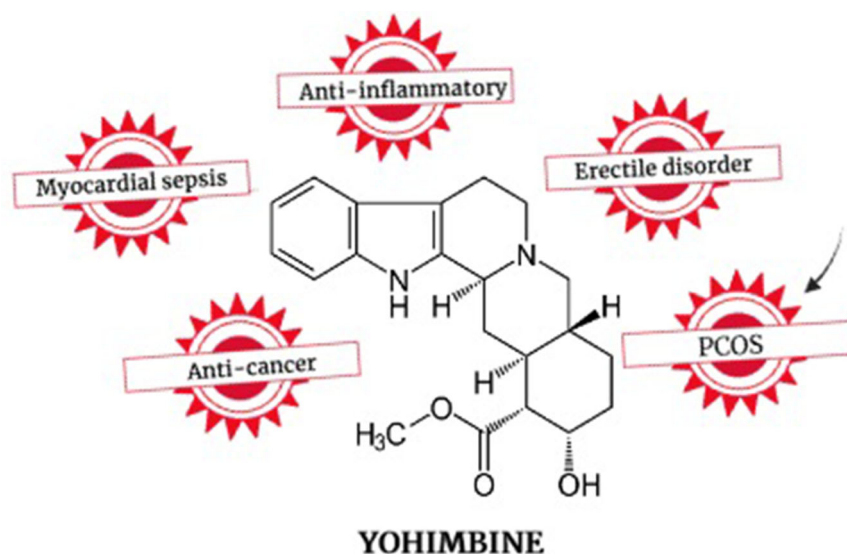
Figure 4. The potential of yohimbine against various human disorders.

losses, m/z 337.1912 caused by H_2O losses, and m/z 397.2108 caused by $C_{10}H_{12}O_5$ losses. Yohimbine has fragment ions at m/z 224.1266, 212.1262, 158.0941, and 144.0802 because of the retro Diels Alder (RDA) cleavage of the C-ring [44]. Duan et al. [32] reported NMR spectroscopy characteristics of yohimbine. These results were comparable with the NMR data of yohimbine previously observed by Herlé et al. [38]. Yohimbine hydrochloride's XRD pattern showed that it has a ring system made up of two transfused six-membered rings D and E connected to two planar indole groups A and B by another six-membered ring C [45].

Pharmacology of yohimbine

The exact physiological mechanisms underlying yohimbine's actions remain unknown. However, the available data suggest its role in sympathetic nerve stimulation [6,46]. Yohimbine stimulates the sympathetic nerve by antagonizing the presynaptic α2-adrenergic receptors (ARs). This action often increases the blood norepinephrine (NE) [46]. The most notable activity of yohimbine is the selective inhibition of ARs; it displays a higher affinity for α2 subtypes and a moderate affinity for the α1 subtypes. Binding affinities among the α2 AR subtypes are reported in the following order: α2C (0.88 nM) >α2A (1.4 nM) >α2B (7.1 nM) [5,47]. The mechanism of action of the adrenergic receptor family has been depicted in Figure 3. Yohimbine also binds other behaviour-related monoaminergic receptors in the following order: α-2 NE > 5HT-1A>, 5HT-1B > 1-D > D3 > D2 receptors [47]. Yohimbine also possesses endothelin-like activities. It influences NO generation and exerts anxiogenic effects via the noradrenergic pathway, activating the hypothalamic–pituitary–adrenal (HPA) stress axis [48,49].

Yohimbine administration also elevates blood epinephrine (EP) and NE in healthy males [46]. It increases the heart rate, systolic blood pressure, alertness, and localized blood flow [50]. An earlier study reported that yohimbine constricts the splanchnic vessels, probably causing blood shunting and hyperaemia of the skeletal muscle [51]. Localized skeletal muscle blood flow modulates the metabolism of the primary energy system and lactic acid production/removal, thus improving anaerobic exercise performance [52]. However, the effect of yohimbine on exercise performance is largely unexplored and requires further investigation.

Yohimbine is rapidly absorbed when consumed orally (absorption half-life: 10 min) and excreted easily (elimination half-life: 30 min) [46]. The therapeutic dose of yohimbine ranges from 50 to 300 ng/mL in the blood [53]. No accurate toxicity or lethal dose data are available for humans except for a few reports on yohimbine fatalities [53]. However, very high concentrations in the blood sample are reported to be toxic. Drevin et al. [53] measured 8000 ng/mL of yohimbine in the blood sample of a 27-year-old male bodybuilder with a history of yohimbine and steroid abuse. The potential of yohimbine against various human disorders is depicted in Figure 4.

Yohimbine for treating erectile disorder

Over the past decades, yohimbine therapy has been used for sexual difficulties. The global prevalence of erectile disorder (ED) represents a significant sexual

difficulty, estimating 300 million men with ED by 2025. Several studies suggest the positive influence of yohimbine on organic impotence [8,54,55]. It is also modestly beneficial over the placebo, particularly in psychogenic erectile disorder, and is generally well tolerated by patients [56]. Guay et al. [54] performed a dose-escalation trial on patients with organic erectile dysfunction and recorded better results when the yohimbine dose was doubled. These patients had minimal side effects, normal cardiovascular responses, and had no significant changes in blood pressure. It was found to be safe for men with medically controlled hypertension. The responders experienced 100% erectile response with satisfactory sexual intercourse compared to the non-responders when 10.8 mg of yohimbine (thrice a day) was administered; the response was independent of age. However, non-smokers and patients with less severe erectile dysfunction responded better. Yohimbine facilitates the ejaculatory function by using the α_1- and α_2-adrenoceptors of the noradrenergic system at the spinal level [57]. Carro-Juárez [57] reported yohimibine involvement in a spinal noradrenergic system controlling the ejaculatory reflex in a rat model by antagonizing the AR-α2. Treatment with yohimbine significantly increased male rats' sexual arousal and mating behaviour without altering the testosterone, FSH, and LH levels [58].

Further, cumulative dose–response curves of yohimbine showed a dose-dependent relaxant effect on isolated rat corpus cavernosum [58]. A recent systematic review and meta-analysis study by Wibowo et al. [8] reported a significant improvement in erectile disorder using yohimbine alone or in combination with other supplements. An earlier study also reported improved erectile function due to the combined treatment of yohimbine and L-arginine, which improved the blood flow, especially in patients with mild to moderate ED [59]. In another study, Senbel and Mostafa [12] reported the yohimbine role in enhancing the impact of sildenafil on the erectile process in a rat model. The combination of the centrally acting yohimbine and the peripheral conditioner sildenafil prolongs the effect of sildenafil on the erectile process without inducing additional hypotension [12].

The smooth muscle constrictor of the corpus cavernosum, relaxant mediators regulated by the central and peripheral nerve systems, and the penis all work together to create the complicated hemodynamic event known as penile erection. The cavernosal tissue and the non-adrenergic non-cholinergic (NANC) system play a major role in erectile response. The degree of erection is determined by the balance between the nitric oxide stimulus generated by non-adrenergic NANC nerves and the counterbalancing of the sympathetic noradrenergic nerves [60]. The action of NE on the α1 and α2 adrenergic receptors in the corpus cavernosum maintains the flaccid state of the human penis [61].

The vasoconstrictor α2-ARs have also been proposed to explain the pro-erectile effects of yohimbine [62]. The mechanical effects of yohimbine (the α2-AR antagonist) induce the pre- and postsynaptic α2-ARs for activating the noradrenergic neurons and releasing NE. This NE, in turn, activates the α-ARs in the endothelium to release NO and prostanoids. These molecules elevate the intracellular cyclic GMP (cGMP) and cyclic CMP, respectively, relaxing the penile smooth muscles. According to Simonsen et al. [63], stimulation of prejunctional α-ARs prevents NO, a NANC neurotransmitter, from being released into penile resistance arteries. Yohimbine inhibits these prejunctional α-ARs, which increases NO production and activates the soluble guanylate cyclase. This raises cGMP levels, which causes the corpus cavernosal smooth muscles to relax [63]. Yohimbine has previously been shown to have a synergistic effect on the *in vitro* relaxing of rabbit corpus cavernosum and the *in vivo* enhancement of rabbit penile erection when the NO pathway is simultaneously stimulated and α-ARs are blocked [64]. Kuchakulla et al. [65] reported yohimbine as an effective ingredient in prevalent over-the-counter testosterone and ED supplements. Yohimbine combined with arginine produces a synergistic effect of increasing the penile artery inflow, acting as a reasonable therapeutic option for ED [66]. Thus, the addition of arginine overcomes the disadvantage of the less-dominant α2-adrenergic receptors in the corpus cavernosum. Despite the reported beneficial effect and mechanistic support, clinical guidelines do not recommend yohimbine as the standard treatment [67]. Yohimbine should be reconsidered as a therapeutic, considering its observed benefits and possible clinical value.

Yohimbine for myocardial dysfunction

Despite some progress in current research, septic cardiomyopathy remains a leading cause of death in the intensive care unit [68]. Identifying therapeutic targets and developing an effective therapy for sepsis-induced myocardial dysfunction is challenging. Lipopolysaccharide (LPS) is an essential activator of pathologic events during septic cardiomyopathy [69]. An earlier study suggested the promoting role of NE in LPS-induced TNF-α production in the Kupffer cells

via α_{2A}-AR stimulation [70]. Other studies also reported increased inflammatory cytokine production through α_{2A}-AR-mediated mechanism of NE in macrophages [71–73]. Blocking the α_{2A}-AR inhibits inflammatory responses and improves the survival of septic rats [74]. The presence of α_{2A}-AR is confirmed in macrophages and LPS-activated macrophages that adhere to cardiomyocytes by reducing the myocardial contractile function via TNF-α and NO [75]. Hence, α_{2A}-AR inhibition in macrophages protects against LPS-triggered myocardial dysfunction.

In an earlier study, Wang et al. [68] reported a role of yohimbine in reversing LPS-induced reduction in left ventricular ejection fraction, stroke volume, cardiac output, and an increment in the left ventricular end-systolic volume. Furthermore, they observed yohimbine-associated prevention of hepatic injury in LPS-challenged mice. In another study, Yu et al. [69] reported reduced septic cardiomyopathy when α_{2A}-ARs were blocked by increasing the cardiac NE concentration and inhibiting cardiac endothelial activation. Wang et al. [76] also reported the beneficial effect of berberine and yohimbine on LPS-induced myocardial dysfunction in mice by inhibiting myocardial apoptosis and I-κBα phosphorylation in the heart. They observed a significantly reversed LPS-induced reduction in the left ventricular ejection fraction and fractional shortening-like control levels by yohimbine, indicating its protective role in systolic myocardial dysfunction. Yohimbine treatment significantly lowered the TNF-α, caspase 3/7, and IL-1β levels in the heart tissue and suppressed LPS-induced myocardial apoptosis. Yohimbine treatment has been reported to reduce cardiac damage. However, no effect was observed on pulmonary injury in LPS-challenged mice, suggesting its organ-specific protective effect [76,77]. A cardiac presynaptic α2A-AR inhibition indicates the cardioprotective effect of yohimbine via inhibition of cardiac iNOS expression and TNF-α production. Yohimbine inhibits α_{2A}-AR and provides a novel therapeutic strategy for myocardial dysfunction in septic patients.

EP and NE profoundly affect platelet aggregation and atherothrombosis. Platelet activation plays a crucial role in the pathogenesis of acute coronary syndrome [78,79]. In one study, Lahiri et al. [80] reported the potency of yohimbine hydrochloride in inhibiting collagen-EP interactive platelet aggregation. They suggested a significant role of α2A-adrenoreceptors of platelets in precipitating the interactive effect of collagen and EP. In another study, Yokota et al. [81] reported the beneficial effect of α2-AR blocking in effectively inhibiting adrenaline-potentiated platelet aggregation. Moreover, Marketou et al. [82] suggested the role of the aggregation regulator α2B-AR subtype in platelets and its inhibition, offering a novel therapeutic opportunity to prevent atherothrombotic events. Kawano et al. [9] recently reported the antiplatelet effect by co-blocking 5-HT2A and α2-AR receptors on the platelets and suppressing platelet aggregation mediated by ADP.

Anti-inflammatory effects of yohimbine

Abnormal immune responses cause inflammatory diseases, and an imbalance between inflammatory mediators and cells leads to chronic or systemic inflammation [83,84]. The scientific community has lately been interested in identifying anti-inflammatory agents from natural resources. Ou et al. [11] reported anti-inflammatory properties of yohimbine that suppress the NF-κB pathway. Yohimbine reduced the IL-1β or noradrenaline-induced IL-6 upregulation and ameliorated cartilage destruction in condylar processes by suppressing the NF-κB pathway in vitro and in vivo. Moreover, yohimbine-induced α2-AR inhibition upregulated tyrosine hydroxylase (TH). Despite intense investigations on TH regulation, effective drugs to upregulate TH are limited. Previous studies showed that α2-AR activation reduced the cAMP levels and increased the cAMP upregulation of TH. These observations indicate a cAMP-mediated mechanism of anti-inflammatory effects [85–87]. Yohimbine also exerts an anti-inflammatory effect by inhibiting pro-inflammatory cytokines and modulating the antioxidant states in arthritic rats [88]. The expression of COX-2, TNF-α, and NF-κB are significantly reduced, and ESR, WBC, and C-reactive protein (CRP) levels are decreased in the rats treated with yohimbine. Moreover, yohimbine provided significant protection from renal ischemia/reperfusion-induced acute kidney injury by blocking of α2 adrenoceptor in a rat model. Recently, Shimokawa et al. [89] also reported the reno-protective effect of yohimbine on LPS-induced acute kidney injury in rats. Yohimbine treatment ameliorates damaged kidney function and LPS-induced low blood pressure; it suppresses cytokine mRNA and iNOS and blocks NF-κB nuclear localization. Yohimbine also enhances the phosphorylation of extracellular signal-regulated kinase (ERK) and cAMP response element-binding protein (CREB) that promotes IL-10 expression. It improved the therapeutic effect of berberine on LPS-induced bacteraemia. This effect is achieved by inhibiting JNK, ERK, NFκB, and other pathways by upregulating IL-10 in a
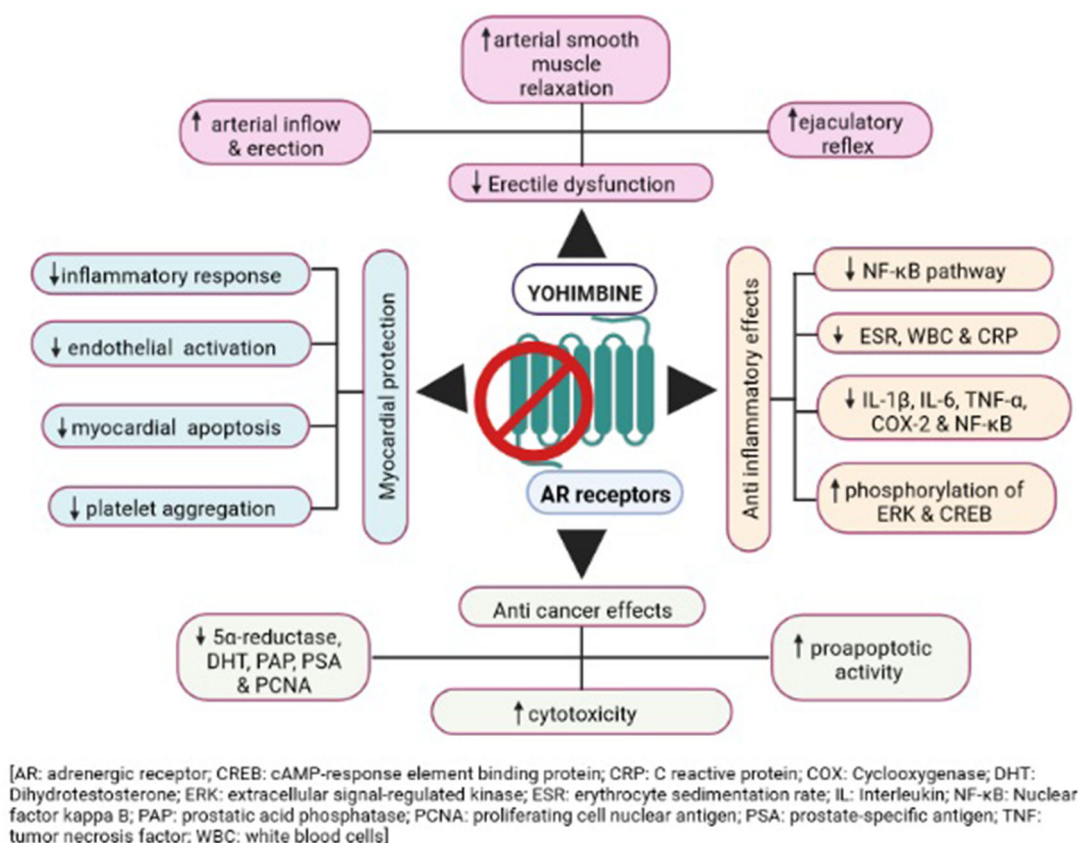
Figure 5. The pharmacological activities and possible mechanisms of action of yohimbine against different human diseases/disorders.

mice model [90]. Thus, the yohimbine–berberine combination is an effective immunomodulating agent. Lin et al. [91] reported that yohimbine inhibits the overproduction of TNF-α, IL-1β, and IL-6 and relieves the severity of pulmonary inflammation induced by endotoxin blockage of α2A AR. Additionally, significant improvements are observed in the oxygenation index, white blood cell count, and lung histopathological scores at each time interval in LPS-treated male Sprague–Dawley rats.

Anticancer effects of yohimbine

The involvement of yohimbine in inflammatory and metastatic pathways has encouraged researchers to evaluate its anticancer potential. Activation of the sympathetic nerves and increased plasma catecholamines indicates higher risk and lower survival of cancer patients due to activated stress response mechanisms [92,93]. Noradrenaline and adrenaline typically orchestrate acute stress reactions and promote other biological processes favourable for stimulating cancer cell proliferation and inhibiting immune surveillance [94]. Several studies reported the probable association

of adrenergic stimulation and carcinogenesis in different cancer forms [95–97].

G-protein-coupled receptors (GPCRs) are promising targets for small molecular therapeutics. They constitute the largest protein superfamily in the human genome and mediate cancer events like proliferation and metastasis [98]. GPCRs are involved in different cancer types such as breast, lung, gastric, pancreas, colon, ovarian, prostate, and melanoma [92,99,100]. Blocking the GPCRs increases the overall survival of cancer patients, thus, indicating their clinical relevance [92]. Yohimbine reportedly inhibits native GPCR targets like the α-2B adrenergic receptor, dopamine D2B receptor, and hydroxytryptamine receptor [47]. A recent study reported antagonistic activities of yohimbine and its ring-distorted derivatives against GPCR-mediated cancer [10]. Additionally, the ring-distorted yohimbine analog Y6p has modest (μM) potencies for the neuropeptide S receptor 1, prolactin-releasing hormone receptor, and follicle-stimulating hormone receptor (IC_{50}=8.03 μM, 10.3 μM, and 4.89 μM, respectively). Another yohimbine analog, Y7g, greatly inhibits the oxytocin receptor (OXTR) and the arginine vasopressin receptors (AVPR1A, AVPR1B, and AVPR2), which are thought to be implicated in the evolution of tumours

in prostate and small-cell lung cancer [10,101]. In contrast to the well-known AVPR2 antagonist, tolvaptan (IC50 = 7.34 pM), Y7g has an IC_{50} of 459 nM and inhibits roughly 83% of the AVPR2 action at 20 μM (in a dose-dependent manner). Same research group also suggested anti-inflammatory and hypoxia-inducible factor-dependent anticancer properties of Y7g [102]. Another analog of yohimbine, Y1f, exhibits antagonistic activity against five GPCRs (≥80% inhibition), including the closely related chemokine receptors CCR3 (IC_{50}=8.30 μM), CCR8 (IC_{50}=7.29 μM), CX3C (CX3CR1, IC_{50}=8.47 μM), C-X-C type 4 (CXCR4, IC_{50}=7.94 μM) and 5-hydroxytryptamine (serotonin) receptor (HTR2C, IC_{50}=180 nM). These GPCRs are expressed in different cancers, and novel antagonists could serve as potential therapeutic targets [10]. Recently, one study reported the therapeutic potential of yohimbine hydrochloride against benign prostatic hyperplasia (BPH) by downregulating steroid 5α-reductase type 2 [103]. Administration of 2, 4, and 8 mg/kg of yohimbine inhibits the increase in the prostatic index by 46.7, 55.1, and 69.3%, respectively, in BHP rats. Furthermore, yohimbine significantly reduces the levels of dihydrotestosterone, prostatic acid phosphatase, prostate-specific antigen, proliferating cell nuclear antigen, and steroid 5α-reductase, suggesting its beneficial effects against BPH. Several studies reported the cytotoxicity of yohimbine in different human cancer cell lines [1,104,105]. Zhan et al. [105] reported moderate cytotoxicity of yohimbine-type alkaloid containing a β-carbolinium group on human MCF-7 breast, SWS80 colon, and A549 lung cancer cell lines with IC_{50} values of 25.5, 22.6, and 26.0 μM, respectively. In addition, Shen et al. [104] reported the proapoptotic activity of yohimbine against the PC-2 and PC-3 pancreatic cancer cell lines. Recently, Yang et al. [1] synthesized novel yohimbine analogs, which showed cytotoxicity against human pancreatic cancer cells (PATU-8988), human gastric cancer cells (SGC-7901), and normal human gastric mucosal cells (GES-1). Yohimbine exerts anticancer effects by inhibiting the GPCRs expressed in the cancer cells [92]. The pharmacological activities and possible mechanisms of action of yohimbine against different human diseases/disorders are highlighted in Figure 5.

Other therapeutic effects of yohimbine

Yohimbine treatment reportedly improves various clinical manifestations of polycystic ovarian syndrome (PCOS), which is treated with insulin-lowering agents. One study reported yohimbine's benefits in reducing PCOS parameters like body weight, LH, and insulin in reproductively mature female rabbits [106]. Increased activities of the sympathetic and HPA axes are reported in PCOS; blocking these pathways is a recommended therapeutic option [107]. In another study, yohimbine therapy reduced the LH concentration and normalized the ovulatory cycles by increasing the oestrogen concentration in PCOS rats [108]. Recently, Barnes et al. [46] reported the beneficial effects of acute yohimbine hydrochloride supplementation on repeated supramaximal sprint performance. Yohimbine also generates and maintains power output during repeated sprints, and its use is recommended for athletes and exercisers to attenuate fatigue and improve anaerobic performance. Nasa and Juneja [109] reported using yohimbine for managing acute pesticide ingestion as rescue therapy. They reported a case of a 3-year-old child who accidentally ingested an amitraz solution and showed signs of severe poisoning. The child regained consciousness after yohimbine treatment in 18 h and was successfully weaned off mechanical ventilation without any side effects. Thus, yohimbine (the α2 adrenergic antagonist) worked as an antidote. It enabled faster neurological recovery, prevented bradycardia, and provided hemodynamic stability in severe amitraz poisoning [109]. Another study reported the weight reduction and anorectic action of yohimbine in a high-fat diet-induced obesity model of rats. Yohimbine reduced body weight and improved lipid and carbohydrate profiles without causing serious side effects [110]. Kotańska et al. [111] reported the favourable influence of yohimbine on the imbalanced lipid carbohydrate homeostasis in leptin deficiency and impairment of the α2- and β3-adrenoceptor function. The overall therapeutic potential of yohimbine and its possible mechanism of action are summarized in Table 2.

Metabolism of yohimbine

Yohimbine shows a comparatively rapid absorption with a half-life of 7–11 min when consumed orally. The plasma levels reach their peak after 45–60 min of ingestion. Around 2.24–1.25 L kg^{-1} of volume is distributed after oral delivery, whereas 0.26 L kg^{-1} is distributed after intravenous exposure [19]. The bioavailability of yohimbine ranges widely from 10% to 90% in humans [112]. Yohimbine is primarily metabolized in the liver, where it undergoes oxidation to its pharmacologically active metabolite 11-hydroxy-yohimbine; a smaller percentage is oxidized to 10-OH-yohimbine [113]. This metabolic pathway depends on

Table 2. Clinical conditions and possible mechanism of yohimbine action.

Disorders	Mechanism of action/clinical effect	References
Erectile disorder	Control ejaculatory reflex in a rat model by antagonizing AR-α_2	[57]
	Dose-dependent relaxant effect in rat corpus cavernosum	[58]
	Improve blood flow and boost erectile function in combination with L-arginine	[59]
	Prolong effect of sildenafil on the erectile process in rat model	[12]
	Maintain a balance between the non-adrenergic, non-cholinergic nerves nitric oxide stimulus, and counterbalance the sympathetic noradrenergic nerves	[60]
	Effective ingredient of testosterone and erectile disorder supplement	[65]
	Synergistic effect of increased penile artery inflow with arginine	[66]
Myocardial dysfunction	LPS-induced TNF-α production *via* α_{2A}-AR	[70]
	Inhibits inflammatory responses and improves septic in rats *via* α_{2A}-AR blockage	[74]
	Reversal of LPS-induced decline in left ventricular ejection fraction, stroke volume, cardiac output, along with an increase in left ventricular end-systolic volume	[68]
	Decrease septic cardiomyopathy *via* α_{2A}-AR blockage and increases cardiac norepinephrine concentration, and inhibit cardiac endothelial activation	[69]
	Inhibit myocardial apoptosis and I-κBα phosphorylation. Reverses LPS-induced decrease in left ventricular ejection and fractional shortening, lowering of TNF-α, caspase 3/7, and IL-1β in the heart tissue. Results cardiac presynaptic α_{2A}-AR inhibition *via* iNOS expression and TNF-α production in combination with berberine	[76]
	Inhibition of collagen-epinephrine interactive platelet aggregation	[80]
	Effectively inhibit adrenaline potentiated platelet aggregation via α2-AR blocking	[81]
	Inhibit α2B-AR aggregation in platelets and prevents atherothrombotic events	[82]
	Co-block 5-HT2A and α2-AR receptors on platelets and suppresses ADP mediated platelet aggregation	[9]
Anti-inflammatory	Suppresses the NF-κB pathway, reduces IL-1β or noradrenaline induce IL-6 upregulation, ameliorate cartilage destruction in condylar processes and upregulate tyrosine hydroxylase	[11]
	Inhibit pro-inflammatory cytokines and modulate antioxidant states, reduces expression of COX-2, TNF-α, and NF-κB, ESR, WBC, and CRP in rats	[88]
	Protect renal ischemia/reperfusion-induced acute kidney injury through blockage of α2-adrenoceptor in rats	[88]
	Reno-protective effect on LPS-induced acute kidney injury in rats and suppresses cytokine mRNA, iNOS, and block NF-κB nuclear localization. Enhanced phosphorylation of extracellular signal-regulated kinase (ERK) and cAMP response element binding protein (CREB) promoting IL-10 expression	[89]
	Immunomodulate and inhibit the JNK, ERK, NF-κB and other pathways *via* upregulation of IL-10 in mice	[90]
	Inhibit TNF-α, IL-1β, and IL-6 overproduction relieving the severity of pulmonary inflammation induced by endotoxin blockage of α2A AR. Also improve oxygenation index, white blood cell count, and lung histopathological scores in rats	[91]
Anticancer	Antagonistic activities against GPCR-mediated cancer	[10]
	Modulate steroid 5α-reductase pathway against benign prostatic hyperplasia by downregulating steroid 5α-reductase type 2 and reduced levels of dihydrotestosterone, prostatic acid phosphatase, prostate-specific antigen, proliferating cell nuclear antigen, and steroid 5α-reductase	[103]
	Cytotoxic with a β-carbolinium group on human MCF-7 breast, SWS80 colon, and A549 lung cancer cell lines with IC50 values of 25.5, 22.6, and 26.0 μM, respectively	[105]
	Induces apoptosis in pancreatic (PC-2 and PC-3) cancer cell lines	[104]
	Cytotoxic against human pancreatic cancer cells (PATU-8988), human gastric cancer cells (SGC-7901), and normal human gastric mucosal cells (GES-1)	[1]
Polycystic ovary syndrome (PCOS)	Reduces PCOS parameters viz. bodyweight, LH, insulin in reproductively mature female rabbits	[106]
	Reduces LH concentration and normalization of ovulatory cycles by increasing the concentration of oestrogen in PCOS rats	[108]
Rescue therapy in acute pesticide ingestion	Regained consciousness, weaned off mechanical ventilation after accidental ingestion of amitraz without any side effects and could serve as an antidote for faster neurological recovery, prevent bradycardia, and provide hemodynamic stability in severe amitraz poisoning	[109]

the cytochrome P450 polymorphic variants CYP2D6 and CYP3A4 [112]. CYP2D6 is a critical drug-metabolizing enzyme that metabolizes approximately 20% of the approved drugs across a broad spectrum of clinical disciplines [114]. CYP2D6 is crucial in eliminating yohimbine *via* 11-hydroxylation; extreme differences exist in yohimbine clearance between the CYP2D6 genotypes. The vast variability observed among individuals in the clinical effects of yohimbine may be attributable to differences in hepatic metabolism. The kidneys excrete yohimbine, and less than 1% of the

medication is found in the urine after 24 h [19]. Yohimbine has a half-life of less than 1 h and is rapidly excreted from the plasma.

Toxicological aspects of yohimbine

Despite well-tolerated effects in both young and elderly populations, scientific reports indicate some dose-related toxicity issues of yohimbine. Generally, yohimbine displays specific side effects like nervousness, insomnia, anxiety, increased urinary frequency,

dizziness, tremors, headache, hypo/hypertension, bronchospasm, and lupus-like syndrome. In rare cases, patients have gastrointestinal symptoms such as nausea, vomiting, lack of appetite, and diarrhoea. The oral administration of yohimbine increases spontaneous salivary secretion in healthy humans [43]. Yohimbine increases NE and its metabolite (3-methoxy-4-hydroxyphenylglycol) in the plasma resulting in hypnotic dysregulation, the most common endocrine effect of yohimbine HCl. These effects may be accompanied by changes in blood pressure, mood, or pulse [115,116]. Yohimbine HCl improves heart performance and increases cardiac output and blood pressure [117]. This effect is dose-dependent and varies widely among individuals. The concentrations of 4–16.2 mg (as a single dose or thrice daily) generally do not affect the blood pressure and pulse in individuals with normal blood pressure. Moreover, 20–30 mg of yohimbine either has no significant effect or moderately increases the blood pressure without affecting the heart rate [6]. On the other hand, concentrations of 45.5 mg and above occasionally increase the medium arterial blood pressure and, less commonly, the heart rate. If such hemodynamic effects occur, they reach their maximum level after 60–90 min and recede over a few hours [6].

Conclusion and future directions

Yohimbine is a prototypical α2-receptor antagonist used widely as a therapeutic agent against erectile dysfunction for many years. It interacts with other behaviourally relevant monoaminergic receptors, viz. α1, 5HT-1A, 5HT-1B, 1-D, D3, and D2. However, the exact mechanism of yohimbine action is unclear. Interestingly, yohimbine compounds meet fundamental drug-like criteria with DPQ and quantitative estimates of drug-likeness. Yohimbine's inhibitory activity on the α2-adrenergic receptor is beneficial in various disease conditions such as erectile dysfunction, myocardial dysfunction, inflammatory disorders, and cancer. However, few studies reported toxicological concerns after yohimbine treatment for erectile dysfunctions, albeit at comparatively higher doses. The potential clinical applicability of yohimbine can be assessed by investigating the relative variables and genetic factors using preclinical models followed by clinical studies. Well-designed randomized clinical trials are recommended to evaluate the efficacy and safety of yohimbine as a human pharmaceutical agent. The extraction or neo-synthesis of yohimbine or its analogs with better bioavailability and limited toxicity is also a possible prospect. Some studies also highlighted a synergetic therapeutic effect of yohimbine with other relevant compounds. Therefore, the possibility of using yohimbine as an adjunct therapy for associated clinical conditions should be tested. Perhaps, nanotechnology can enhance the effectiveness and bioavailability of yohimbine in diseased cells by preventing the disruption of normal physiological activities of non-diseased cells and organs. Despite some observed adverse effects, yohimbine use should be reconsidered for its associated benefits and clinical value.

Author contributions

ST, TAZ, and BA: Conception and design, and interpretation of the reported data; NRJ, CKF, MAA, and AA: Drafting of the paper; ST, AMA, AIA, BA, and AA: Revised critically for intellectual content, ARK; and the final approval of the revised version. All authors agree to be accountable for all aspects of the work. All the authors listed in this article meet the criteria for authorship as per the ICMJE.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Data sharing not applicable—no new data generated.

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