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Review Article on Phytochemical Constituents and Biological Activity of *Artemisia Annua* L.

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ABSTRACT

Artemisia annua is an aromatic plant belonging to the Asteraceae family, found around Africa, Asia, Europe, and North America. The World Health Organization has recommended A. annua as an antimalarial drug. Numerous phytochemical classes, such as phenolics, flavonoids, steroids, coumarins, triterpenoids, monoterpenoids, lipids, aliphatic compounds, lignans, as well as fatty acids, have been found through phytochemical investigation. The plant was chosen due to a well-researched biological study that revealed it to have antimalarial, antioxidant, antimicrobial, antiviral, anti-inflammatory, anticancer, and immunosuppressive activity. This review focuses on the phytochemical components of this significant and beneficial plant, as well as the various promising biological activities that make the plant a good candidate for developing pharmaceutical products. Definitively, the plant extract of A. annua is a good source of health-promoting aspects that can be employed for curative and nutritional purposes. However, more research on the active chemicals of this plant is needed to optimize their medicinal and nutritional potential.

KEYWORDS: Artemisia annua, Asteraceae, Phytochemicals, Biological.

1. INTRODUCTION

The Asteraceae family includes a huge number of genera, among which Artemisia is one of the largest and most widely distributed [1]. Artemisia L. is a widespread genus with around 500 species distributed throughout all continents except Antarctica. The genus adapts to many environments from sea level to high altitudes [2].

Artemisia annua, a plant belonging to the Asteraceae family, is a widely used medicinal plant [3-5], sometimes known as "annual absinthe". It is an annual herbaceous plant, thus its name "annua." The plant is grown in Asia, India, Central and Eastern Europe, in the temperate regions of America, Africa, and Australia, as well as in tropical regions [6, 7]. In the mild climates of Asia (specifically China and Korea), it is widely utilized as a medicinal plant, herbal tea, and spice in food [8]. Qing Hao is an ancient Chinese name for A. annua, which means "green herb. There are two main hypotheses on the origin of name. According to the first theory, Artemisia is named after the Greek goddess "Artemis", which means "she who heals sickness." According to a second theory, it was named after the queen of Turkey, Artemisia of Caria [9]. For many years, the traditional medical practices of Asia and Africa have utilized A. annua, either as squeezed juice or tea, to cure fever and malaria [10, 11]. The dried herb A. annua is officially listed as a treatment for fever and malaria in China's current pharmacopeia. The

recommended daily dosage is 4.5–9 g of dry herb made as an infusion [12]. Additionally, A. annua has anti-hyperlipidemic, anti-plasmodial, anti-convulsant, anti-inflammatory, anti-microbial, anti-cholesterolemic, and antiviral effects [13-15]. It also has essential pharmacological properties such as being anticancer, as well as anti-obesity [16-18].

Several bioactive metabolites have been found in A. annua. Artemisinin is the lactone sesquiterpene endoperoxide that has been investigated the most [19]. Because of its antimalarial properties, artemisinin is effective against chloroquine-resistant Plasmodium falciparum in the treatment of cerebral malaria [20, 21]. Several thousand malaria patients in China have benefited from the use of this substance, beside those who were infected with strains of Plasmodium falciparum that were resistant to chloroquine. Artemisinin presents a promising new class of antimalarial medication [22]. In addition to this active compound, A. annua has an interesting nutritional profile that includes amino acids, vitamins and minerals, as well as other important elements for health [23]. A. annua has been the subject of extensive research on its chemical composition since its discovery. Over 600 secondary metabolites have been discovered throughout the plant [24], including a number of steroids, flavonoids, coumarins, alkaloids, benzenoids, triterpenoids, and monoterpenoids [3, 25, 26].

The purpose of this review was to provide a comprehensive overview of A. annua's traditional use and pharmacological studies, as well as innovative insights into its use in the treatment of numerous diseases.

2. MATERIAL AND METHODS

Using well-known scientific resources including Google Scholar, Scopus, Science Direct, Henriette's Herbal Homepage, PubMed, King's American Dispensatory, Ethnobotanical Databases, Dr. Duke's Phytochemical and SciFinder, this review carefully reviewed the material that was available. Books on taxonomies and ethnopharmacology that were available were consulted for specific details. The Plant List (http://www.theplantlist.org) was used to obtain this data. After collating the published papers, the findings were examined and organized through the theme of the portion or review. A total of eighty published papers were gathered, and the library of publications retrieved included materials that were either published before 1990 (ten), or not written in English (eight).

3. RESULTS AND DISCUSSION

3.1. Chemical Constituents Reported from *Artemisia annua*

Phytochemical investigation of Artemisia annua revealed the presence of many bioactive compounds, such as flavonoids, coumarins, phenolics, terpenoids, steroids, phenolic acid derivatives, alkyl alcohols, fatty acids, lipids, Lignans and essential oils (Table 1).

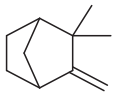
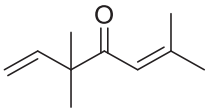
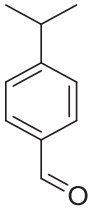
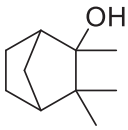
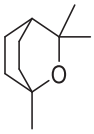
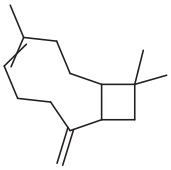
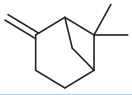
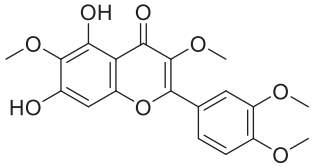
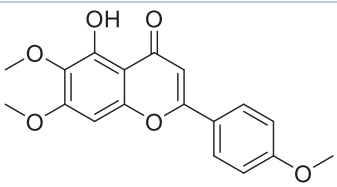
3.1.1. Essential Oil

A. annua is known to consist of both volatile and non-volatile components. Among the volatile components are camphene, β-caryophyllene, β-pinene, artemisia ketone, 1, 8-cineole, camphene hydrate, and cuminal [27].

3.1.2. Flavonoids

Flavonoid is one of the major phytoconstituents detected from A. annua including quercetagetin 3,6,3`,4` tetramethyl ether, salvigenin, 5,4` dihydroxy 3,3`,7 trimethoxy flavone (pachypodol), artemetin, rutin, chrysosplenetin, 5 hydroxy 3,7,3',4' tetramethoxy flavone, 5 hydroxy 6,7,8,4' tetramethoxy flavone [28], and casticin [29].

Table 12: Examples of some compounds isolated from *Senna*

Compound	Structure	Biological Activity	References
Camphene		Anti-viral Anti-leishmanial	[27,48,49]
Artemisia ketone		Anti-bacterial	[27, 50]
Cuminal		Antioxidant	[27, 51]
Camphene hydrate		Anti-microbial	[27, 52]
1, 8-cineole		Cytotoxic activity	[27, 53]
β-caryophyllene		Anti-bacterial	[27, 54]
β-pinene		Anti-microbial	[27, 55]
Quercetagetin-3,6,3`,4`-tetramet h ether		Antioxidant	[28, 56]
Salvigenin		Anti-inflammatory Analgesic properties	[28, 57]

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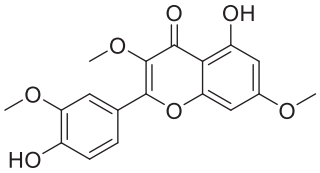
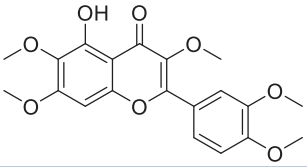
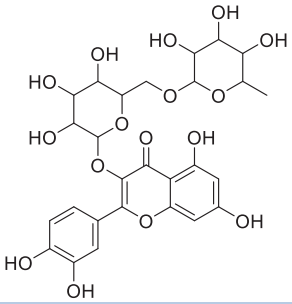
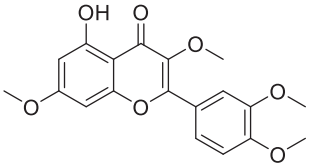
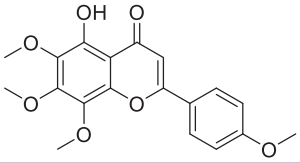
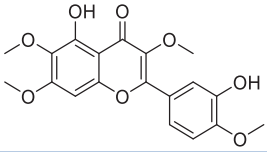
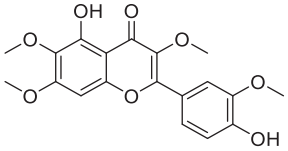
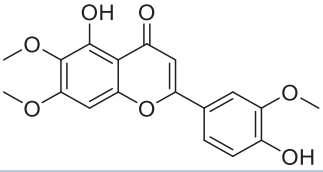
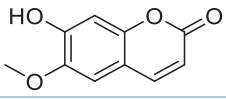
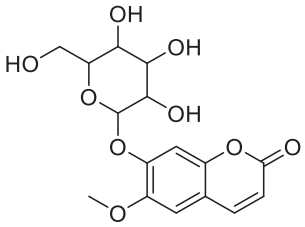
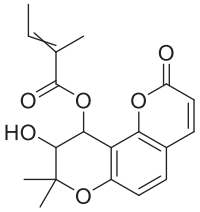
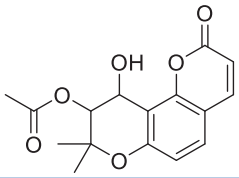
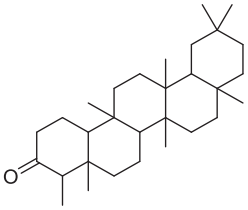
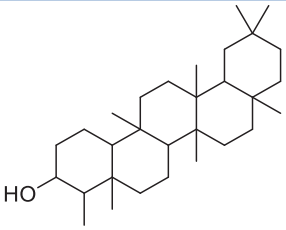
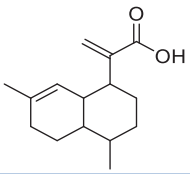
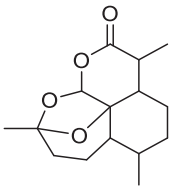
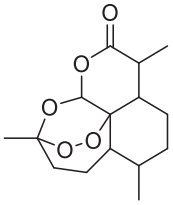
5,4`-dihydroxy-3,3`,7-trimethoxy flavone		Antioxidant Androgenic potential	[28, 58]
Artemetin		Anti-edematogenic	[28, 59]
Rutin		Anti-amyloidogenic Antioxidant	[28, 60]
5-hydroxy-3,7,3`,4`-tetramethoxy flavone		Anti-fungal	[28, 61]
5-hydroxy-6,7,8,4'-tetramethoxy flavone		Anti-bacterial Anti-fungal Insecticidal activities	[28, 62]
Casticin		Anti-osteoporosis Cytotoxic activity	[29, 63]
Chrysosplenetin		Anti-viral	[28, 64]
Cirsilineol		Anti-bacterial	[65, 66]
Scopoletin		Anti-fungal Anti-hypertensive	[30,67,68]

Scopolin		Anti-ulcerogenic	[30, 69]
Qinghaocoumarin A		Anti-fungal	[25]
Qinghaocoumarin B		Anti-fungal	[25]
Friedelin		Anti-hyperglycemic Anti-malarial	[32,70,71]
Friedelan -3-ol		Anti-ulcerogenic	[32, 72]
Artemisinic acid		Anti-inflammatory Anti-mycobacterial	[32,73,74]
Deoxyartemisinin		Anti-mycobacterial	[32, 74]
Artemisinin		Anti-viral	[31, 75]

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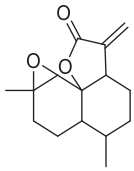
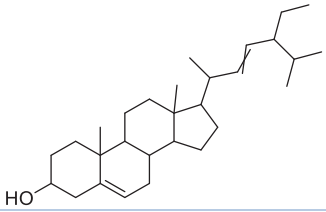
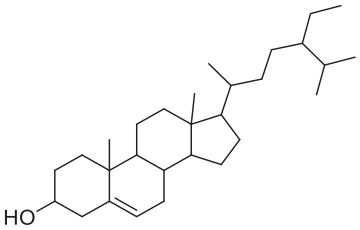
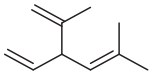
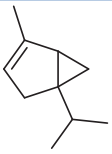
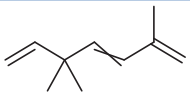
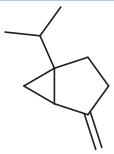
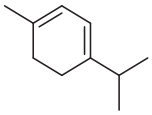
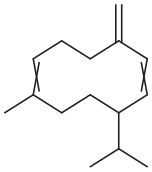
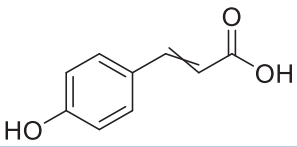
Arteannuin B		Cytotoxic activities Anti-fungal	[31,76,77]
Stigmasterol		Anti-microbial Cytotoxic activities	[31,78,79]
β-sitosterol		Anti-bacterial anti-inflammatory	[31,80,81]
Santolina triene		Anti-inflammatory Antioxidant Anti-bacterial	[33, 82]
Tricyclene		Anti-platelet Anti-bacterial	[33, 83]
α-thujene		Antioxidant Cytotoxic activities	[33, 84]
Artemisia triene		Anti-microbial **Antioxidant**	[33, 85]
Sabinene		Anti-fungal Antioxidant Anti-inflammatory	[33, 86]
α-terpinene		Antioxidant	[33, 87]
Germacrene D		Anti-bacterial	[33, 88]
p-coumaric acid		Anti-angiogenic	[34, 89]

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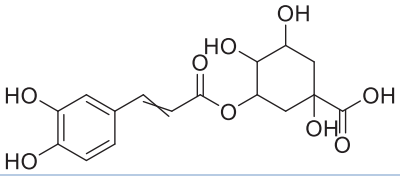
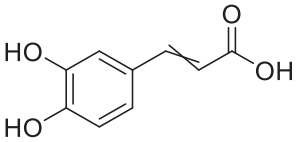
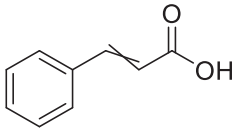
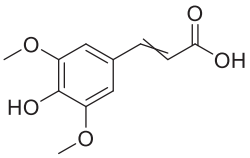
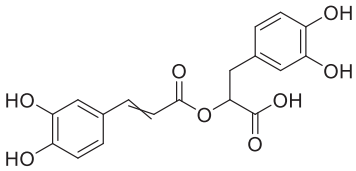
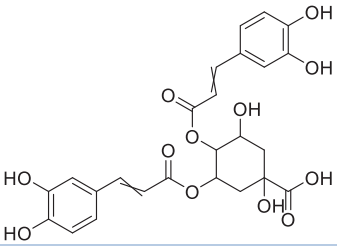
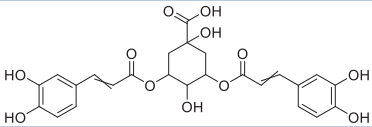
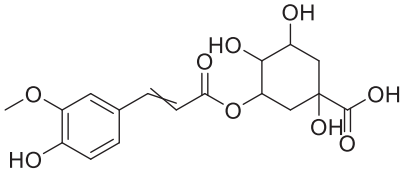
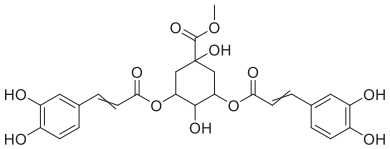
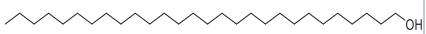
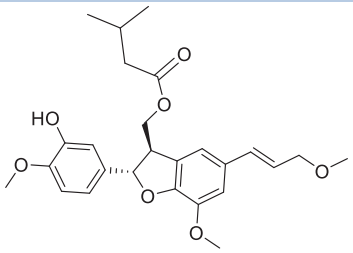
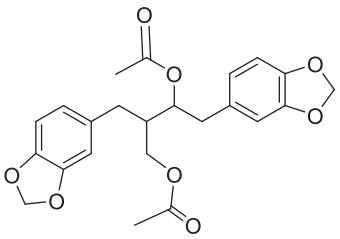
Chlorogenic acid		Anti-bacterial	[34, 90]
Caffeic acid		Diabetic Neuropathy Antioxidant Anti-inflammatory	[34, 91]
Cinnamic acid		Anti-microbial	[34, 92]
Sinapic acid		Antioxidant Anti-inflammatory Cytotoxic activities Anti-mutagenic Anti-glycemic	[34, 93]
Rosmarinic acid		Cytotoxic activities Epileptiform activity	[35,94,95]
3,4-Dicaffoeylquinic acid		Hepatoprotection Anti-hyperglycemic Antioxidant	[36].
3,5-Dicaffoeylquinic acid		Hepatoprotection Anti-hyperglycemic Antioxidant	[36].
3-Feruloylquinic acid		Hepatoprotection Anti-hyperglycemic Antioxidant	[36].
3,4-Dicaffoeylquinic acid methyl ester		Hepatoprotection, Anti-hyperglycemic Antioxidant	[36].
Docosan-9β-ol		Antiviral	[37, 96]
1-octacosanol		Insecticidal Juvenomimetic	[37, 97]

n-nonadecan-2*β*-ol		Anti-inflammatory	[37, 98]
QinghaolignanA		Anti-fungal	[25]
QinghaolignanB		Anti-fungal	[25]

3.1.3. Coumarins

Some coumarins were founds in A. annua such as scopolin (coumarin glycoside), and scopoletin [30] in addition to two new coumarin (qinghaocoumarin A and (±)-qinghaocoumarin B) that were also isolated from A. annua [25].

3.1.4 Terpenoidal and Steroidal Compounds

From A. annua, Tang et al. isolated some cadinane compounds, artemisinin and arteannuin B, as well as β-sitosterol, and stigmasterol [31]. Zheng et al. detected artemisinic acid, deoxyartemisinin, friedelin, and friedelan 3β-ol [32]. Ruan et al. isolated monoterpenes including santolina triene, tricyclene, artemisia triene, α-thujene, α-terpinene, germacrene D, and sabinene [33].

3.1.5 Phenolic Acid Derivatives

In the study of A. annua, hydroxycinnamic acids were discovered consisting of p-coumaric acid, chlorogenic acid, caffeic acid, cinnamic acid, sinapic acid [34], as well as rosmarinic acid [35]. Quinic acid derivatives, including 3,4-dicaffoeylquinic acid, 3,5-dicaffoeylquinic acid, 3-feruloylquinic acid and 3,4-dicaffoeylquinic acid methyl ester, were isolated from A. Annua [36].

3.1.6 Alkyl Alcohols, Fatty Acids, and Lipids

Phytochemical analysis of A. annua revealed the presence of alkyl alcohols, such as docosan-9β-ol, 1-octacosanol, and n-nonadecan-2β-ol [37]. In addition to the detected fatty acids from A. annua, including myristic acid, palmitic, palmitoleic, oleic acid, stearic acid, α-linolenic, and linoleic, other lipids have also been determined, like γ-tocopherol, and α-tocopherol [38].

3.1.7 Lignans

Two new lignans, qinghaolignan A and qinghaolignan B, were also isolated from A. annua [25].

3.2. Biological Activities Reported from *Artemisia annua*

3.2.1. Antimalarial Effect

Artemisia annua aqueous and hydroalcoholic extracts were tested for antimalarial activity both in vitro and in vivo. These extracts were made by decoction and maceration using water and ethanol and were investigated for in vitro activity against Plasmodium falciparum strains. The extracts were further tested in vivo against Plasmodium berghei NK 173-infected mice using the 4-day suppression test. These extracts acted similarly in vitro to pure artemisinin at the same dose. However, in vivo investigations on mice reveal that we achieve the same efficacy with an aqueous extract of A. annua (artemisinin content of 20 mg/kg) than with pure artemisinin at a dosage of 140 mg/kg. The hydroalcoholic extract of A. annua (artemisinin concentration of 20 mg/kg) outperformed the two other conditions [39].

3.2.2 Anti-inflammatory effects

A. annua was first reported to have anti-inflammatory effects in 1993 in rat and mouse inflammatory models induced by dimethylbenzene (auricle smear method), egg white (injection under the aponeurosis), and yeast powder (injection under the aponeurosis). When taking A. annua water extraction (15, 30, and 60 g/kg) orally for four or six days in consecutive days, inflammatory responses dramatically decrease [40]. An in vitro study evaluated the anti-inflammatory activities of four artemisinin-containing extracts of A. annua (water, methanol, ethanol, and acetone). Acetone extract (100 μg/mL) with the highest artemisinin content inhibits Lipopolysaccharide (LPS)-activated nitric oxide (NO), prostaglandin E2 (PGE2), and pro-inflammatory cytokine interleukin (IL-1β, IL-6, and IL-10) production in RAW 264.7 macrophages [41].

In Chougouo's investigation, similar results were obtained; the research extracts ethanol at the concentration of 6.25, 12.5, 25 and 50 μg/mL, and five isolated components (scopoletin, 3- O-β-D-glucopyranoside of sitosterol, chrysosplenetin, artemisinin, and eupatin) at the concentration of 0.5, 2, 5 and 20 μg/mL all inhibited the production of NO in LPS-induced RAW 264.7 macrophages [42].

3.2.3. Anti-viral Activities

The volatile oil from A. annua was extracted and hydroxypropyl-β-cyclodextrin inclusion complex was produced. The volatile oil of A. annua was found to have anti-viral properties against RSV and Coxsackievirus 16 (CA16), with EC50 values of 3.12 and 9.14 μg/mL, respectively. The hydroxypropyl-β-cyclodextrin inclusion complex of the volatile oil had EC50 values of 0.28 and 0.59, respectively [43].

Artemisinin levels in various A. annua tea samples were analyzed, revealing that the most active sample had one of the lowest concentrations, while the highest content sample had the lowest activity. Pure artemisinin was inert at 25 μg/mL. The study found that artemisinin played a minor impact in A. annua is an anti-HIV activity. The methanol extract of A. annua had a mild inhibitory effect on virus-cell infusion (15.8%), potentially explaining its anti-viral activity [44].

3.2.4 Anti-cancer Activities

Artemisinin and its derivatives have been shown to have anti-cancer effects by arresting cancer cell proliferation, increasing apoptosis, and blocking tumor angiogenesis and invasion

[45]. A. annua extract contains chrysosplenol D, arteannuin B, and casticin, which limit cell proliferation, cause apoptosis, and reduce tumor growth. This indicates a possible anti-cancer efficacy. Meanwhile, the anti-cancer properties of dried leaf A. annua and artesunate against NSCLC cell line were evaluated at the same dose of comparable molar artemisinin [46]. Casticin and chrysosplenol D are two flavonoid compounds known to have anti-cancer properties. Casticin, a polymethoxy flavone present in many herbal plants, had a concentration of 1.07 ± 0.23 mg/g in A. annua [30].

3.2.5 Anti-asthmatic Activities

The chloroform extract of A. annua reduced high K+-induced contraction in mouse TRs in a dose-dependent manner (IC50 = 0.316 mg/mL). A chloroform extract of A. annua can also inhibit acetylcholine -induced contractions. Patch clamp technique and ion channel blockers were used to investigate the underlying mechanisms of A. annua's anti-asthmatic activity. Results showed that blocking voltage-dependent Ca2+ channel-mediated Ca2+ influx was crucial, while enhancing Ca2+-activated K+-mediated K+ conductance was less important [47].

3.2.6 Immunoregulation Activities

Ethanol extract of A. annua at concentrations of 1–100 μg/mL significantly reduced the splenocyte proliferations stimulated by concanavalin A (Con A) and LPS in a concentration-dependent manner. Moreover, in ovalbumin-immunized mice, intraperitoneally administration of A. annua ethanol extract at a single dose of 0.25, 0.5 and 1.0 mg significantly reduced the ovalbumin-specific serum lgG, lgG1 and lgG2b antibody levels and suppressed the splenocyte proliferation. Taken together, A. annua did showed immunoregulation activities, but it deserved more studies to be developed as immune modulator [47].

4. CONCLUSION

A comprehensive examination of the phytochemistry, pharmacological activities, and historical significance of A. annua is presented in this review. Phytoconstituents showing great therapeutic promise for the treatment of a range of infectious and degenerative disorders have been identified by the investigations. Numerous studies on the pharmacology of the A. annua. have supported the known traditional uses of the plant. As a result, it is critical to carefully examine isolation and clinical trials, as they may result in the discovery of novel bioresources and satisfy scientists' biotechnological needs for safe therapeutic drugs to treat today's health challenges.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX A: LIST OF ABBREVIATIONS

EC50	Half maximal effective concentration
g	Gram
HIV	Human immunodeficiency virus
IC50	Half maximal inhibitory concentration
IgG	Immunoglobulin G
IL-10	Interleukin 10
IL-1β	Interleukin-1 beta
IL-6	Interleukin 6
Kg	Kilogram
LPS	Lipopolysaccharide
mg	Milligram
mL	Millimeter
NK	Natural killer
NO	Nitric oxide
NSCLC	Non-small cell lung cancer
PGE2	Prostaglandin E2
RSV	Anti-respiratory syncytial virus
TC221 cells	Trypanosoma brucei cell line
TRs	Tracheal rings
Mg	Microgram