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THE PLANT *ARTEMISIA ANNUA* ("SWEET WORMWOOD") KAZAKHSTAN'S SOURSE OF BIOACTIVE COMPOUNDS POTENTIALLY CURE THE SARS-COV-2 INFECTION

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ABSTRACT

The genus Artemisia ("wormwood") is widely represented in the flora of Kazakhstan both by the species diversity (at least 80 species) and biomass. Members of this genus, such as *Artemisia annua* («annual wormwood») attract the attention of the global biomedical community because these plants produce the unusual sesquiterpene lactone artemisinin, which has a proven efficacy as an antimalarial drug and has also been tested for antiviral activity. Due to their potential antiviral properties, wormwood-derived phytocompounds are of interest as promising drugs against the SARS-CoV-2 coronavirus, which caused the largest pandemic of the 21st century. This review presents the studied diversity of secondary metabolites synthesized by various Artemisia species, describes the actual practical significance of one species *A. annua*, as well as the possible use of substances from this species as antiviral agents. There is a need for further research into secondary metabolites of wormwood with antiviral properties due to the expectation of continued circulation of the SARS-CoV-2 virus and in order to complement the arsenal of antiviral therapy.

Keywords: Artemisia annua; sesquiterpene lactone; artemisinin; antiviral activity; SARS-CoV-2

INTRODUCTION

The coronavirus SARS-CoV-2 has caused pandemic which is now in its third year as of mid-2022. As pandemic restrictions are gradually eased, it is becoming increasingly clear that this epidemiological event has caused an enormous damage to social life and the economy across the world [1]. The development of the pandemic in the future looks like SARS-CoV-2 will not disappear from human populations [2]. A corollary of data already published proves that the SARS-CoV-2 virus efficiently evades the restricting factor of herd immunity [3,4] with has a consequence that this virus will continue to circulate even in communities with a high proportion of vaccinated and convalescents [5]. It is more expected that SARS-CoV-2 will become similar to seasonal human coronaviruses. If this is the case, then new cases of SARS-CoV-2 infection or seasonal outbreaks of SARS-CoV-2 will be recorded in indefinitely long future [6,7].

The success of mass vaccination campaigns and increasing fractions of convalescents supposedly have resulted in the stronger herd immunity and decreasing hospitalizations and deaths. Realistically, as with other pneumonia-causing respiratory infections some future SARS-CoV-2-patients will worsen to severe pneumonia and acute respiratory distress syndrome (ARDS) and will depend on an intense therapy. The task of finding effective and affordable drugs to treat the SARS-CoV-2 disease is important now and will be that in the future [8]. One focus in the continuing research is on drugs with a direct antiviral action (direct-acting antivirals, DAA) [9]. The DAA class represents compounds capable of specifically recognizing SARS-CoV-2-virus proteins at the molecular level, binding these viral targets and inhibiting their specific functions. However, to date the search for effective DAA against SARS-CoV-2 had a limited success. A number of drugs had been registered previously to other indications and now they are repurposed to treat SARS-CoV-2. Some of these drugs show the antiviral effect against SARS-CoV-2 in *in vitro* experiments but a number of the repurposed drugs which have shown clinical efficacy in properly organized randomized controlled clinical trials is scarce [10].

A list of drugs in the DAA class clinically approved to treat the SARS-CoV-2 disease is just small [11]. A regulatory agency FDA in the USA has granted an unrestricted clinical approval only for Remdesivir [12]. Remdesivir is a synthetic inhibitor of viral RNA polymerase belonging to the class of nucleotide analogs. The Emergency Use Authorization (EUA) was given for five therapeutic monoclonal antibodies capable of neutralizing the SARS-CoV-2 virus: Casirivimab, Imdevimab, Sotrovimab, Bamlanivimab and Etesevimab [13]. Among low-molecular-weight compounds, a different drug Paxlovid has had the EUA [14]. Paxlovid is a mixture of two synthetic compounds which are inhibitors of the main viral protease Mpro. However recently the EUA was revoked from Paxlovid because Paxlovid appeared to be ineffective against the strain omicron (SARS-CoV-2 omicron) which currently dominates the circulation. Some other drugs such as anti-inflammatory steroid dexamethasone are also recommended in SARS-CoV-2-treatment protocols but these drugs are not DAA and not a focus of this review.

In a larger part of Eurasia, the only clinically approved DAA for SARS-CoV-2 is Favipiravir. Favipiravir is present on the market under different brand names: Avifavir, Areplivir, Coronavir. The published literature on Favipiravir convinces that this substance is not a highly active inhibitor of the SARS-CoV-2 replication [15]. Accordingly, the reported clinical benefits from Favipiravir are marginal. In one clinical trial, Favipiravir reduced the time of hospital stay for patients with moderate SARS-CoV-2 pneumonia by two days (11.9 days in the favipiravir group vs. 14.7 days in the placebo group, this difference was statistically significant). Favipiravir has significant toxicity at therapeutic doses and exerted measurable adverse effects [16]. The half-maximum (50%) effective concentration of Favipiravir in *in vitro* tests (EC_{50}) is high, >60 µM. This requests large doses in the treatment, 3600 mg in the first day, then 1600 mg per day for 13 days. Still the regulatory authorities in the majority of Eurasian countries including Kazakhstan have approved the use of Favipiravir to treat SARS-CoV-2. It is probably because of the pressure of a desperate quest for a DAA drug to fight the disease in heavy cases considering a lack of efficacious alternatives.

Kazakhstan and the whole region of Central Eurasia suffered a significant damage from SARS-CoV-2. The access of patients in Kazakhstan to SARS-CoV-2 drugs in the DAAs is limited because the clinical-trials-proven drugs such as Remdesivir are not available on the local market.

Biologically active compounds of the plant origin with a potential DAA activity against the SARS-CoV-2 virus are actively searched for [17, 18]. In particular, a variety of herbs or small bushes colloquially known as “mugwort”, “wormwood” or “sagebrush” and botanically classified within the genus Artemisia, family Asteraceae, are the potential source of the needed substances. The wormwood plants (*Artemisia spp*.) have served for centuries as sources of traditional medicines for the treatment of malaria, hepatitis, cancer, inflammation and infections caused by pathogenic fungi, bacteria and viruses [19].

The goal of this review is to present the genus Artemisia and its species which are currently considered to be the most important in the search for natural DAA drugs against SARS-CoV-2.

Secondary metabolites in *Artemisia spp.* The genus Artemisia comprises 441 species with subspecies as is the modern taxonomic classification embedded in the NCBI Taxonomy platform.

Due to the ancient history of usage in traditional medicine and the ever-proven importance of some wormwood species for the culinary, cosmetics and other human needs *Artemisia spp*. attracted much attention of chemists studying the biosynthesis of secondary metabolites. Unlike primary metabolites which directly participate in cellular or organismal growth, development and reproduction, secondary metabolites are not necessarily involved in these processes. The secondary metabolites in plants are low-molecular-weight compounds which are typically synthesized at defined stages of development for accessory purposes such as to repel pests or ruminants, to attract cross-pollinators, or as antimicrobials fighting plant pathogens.

Among wormwood species *Artemisia annua* (Figure 1) is a leader by the number of individual chemical compounds identified in the plant or its extracts, essential oils, etc. [20].

This interest from biochemists is because *A. annua* contains substances which currently have a prominent position in the world’s pharmacology as anti-malaria drugs [21]. Table 1 lists several widely-known Artemisia species which have a long-term consumption in different cultures. The data in this table contain numbers of individual structures of secondary metabolites which were identified in different species. It must be noted that the varying numbers of the identified compounds are not because some species are rich in the secondary metabolites and others are poor. Rather the data reflect an unequal interest towards particular species from researchers and technically equipped laboratories capable of separating ad indentifying plant compounds. Long lists of secondary metabolites

Figure 1 - The photo of *Artemisia annua L.* plant.
(Image from https://commons.wikimedia.org/wiki/File)

which can be extracted from different *Artemisia spp*. have been published [22, 23].

Not all compounds which can be detected by sensitive physico-chemical methods such as gas chromatography/mass spectrometry (GC-MS) actually have the concentration allowing expecting the compound will show a biological activity at that concentration. With this regard, one detailed review [19] provides important information on the major constituents present in amounts no less than 10% in an essential oil (plant extract). In Artemisia, all the major constituents belong to classes of oxygenated polyene compounds containing one or several aromatic or aliphatic cycles with no heteroatoms except occasional oxygen. These are terpenes, phenols and lactones, some are flavonoids and carboxylic acids of the above. One important major class of Artemisia-derived substances for which the antiviral activity was confirmed and systematically studied is sesquiterpene lactones [24]. No alkaloids (alkaloid is a natural nitrogen-containing heterocyclic compound) were found in abundance >10% in the Artemisia essential oils.

A different study describes the following content in *A. annua* extracts: monoterpenes (28 chemically different compounds), sesquiterpenes (30 compounds), triterpenoids and steroids (12), flavonoids (36), coumarins (7), aromatic (4) and aliphatic (9) compounds [27].

Artemisinin, related compounds and other Artemisia sesquiterpene lactones. Importantly *A. annua* and 13 other species according to the Pubchem database but not the majority of other species in this genus produce and accumulate artemisinin. The discovery of artemisinin brought the Nobel Prize in Physiology or Medicine to the Chinese researcher Youyou Tu in year 2015 [25]. Artemisinin is undoubtedly the most

Table 1 - Selected wormwoods species of the genus Artemisia and the number of individual chemical compounds identified in the plants

Species	Trivial name	Geographic area [1]	Number of chemical compounds [2]	TaxID number at Pubchem [3]	Most known fact about the species
Artemisia annua L.	"sweet wormwood", "annual mugwort" (English), "qinghao" (China)	Eastern Europe, Eastern and Central Asia, also widely introduced in other world regions	330	35608	Contains artemisinin which is the WHO-approved anti-malaria drug
A. absinthium L.	"wormwood"	Asia, Europe, Middle East, North Africa	125	72332	Absinthe (alcoholic spirit) is made from this species
A. abrotanum L.	"southernwood"	Asia, Europe, Mediterranean	33	86306	
A. afra Jacq. ex Willd.	"wilde als"	South Africa	31	72333	
A. douglasiana Besser	"california mugwort"	North America	37	1227621	
A. princeps Willd	"Japanese mugwort" (English), "yomogi" (Japan)	Japan	53	223870	Used in traditional Japanese sweets "kusa-mochi"
A. echegaray Hieron	"ajenjo"	South America	0	927721	
A. dracunculus L.	"tarragon"	Eastern Europe, Asia	0	401895	Common spice. Well-known as "estragon" or "tarkhun"

Comments: [1] geographic regions of the natural inhabitance are listed; however, some wormwood species have been introduced in the culture and are currently grown in different regions of the world beyond their natural habitat. [2] a number of different individual chemical compounds which have been identified in the plant or its extracts. The number is extracted from the Pubchem (https://pubchem.ncbi.nlm.nih.gov/) database. [3] The NCBI taxonomic ID can be used to extract the information on chemical compounds found in particular species, use the link https://pubchem.ncbi.nlm.nih.gov/taxonomy/NNNNNN, where NNNNNN is the TaxID.

practically important chemical derived from the whole genus Artemisia. This is because artemisinin and its semi-synthetic derivatives have been recommended by the World Health Organization (WHO) as an effective treatment to malaria caused by the parasitic single-cell eukaryote *Plasmodium falciparum* [26].

Artemisinin (Figure 2) is a sesquiterpene lactone having an unusual intramolecular endoperoxide (C-O-O-C) bridge [24]. This endoperoxide group was shown to be directly involved in the drug's action against malaria.

The amounts of artemisinin in *A. annua* plants is low in general. The low content in the natural source is a reason why artemisinin is not listed as among substances commonly found in *A. annua* essential oils [19]. Also, the artemisinin content varies considerably in a range 0.01-1.5% by dry weight of plant material because the artemisinin accumulation is highly dependent on plant's genetics and other factors. The artemisinin presence is maximal in leaves. There are different cultivars or chemotypes of *A. annua* with the quite different production [27, 28]. The best cultivars can provide 1.5% artemisinin in dry leaves translating to yields per hectare 70 kg/ha. However, common seed-propagated *A. annua* plants typically produce <1% (by dry weight) artemisinin and the yields are <25 kg/ha [27]. Plant growing conditions themselves strongly affect the artemisinin content [29]. Collected leaves must have artemisinin at least 0.6% (dry weight) for the extraction to be economically justified. Artemisinin is a difficult target for chemical synthesis although some fully synthetic pathways were proposed [30]. The artemisinin production in cultured plant

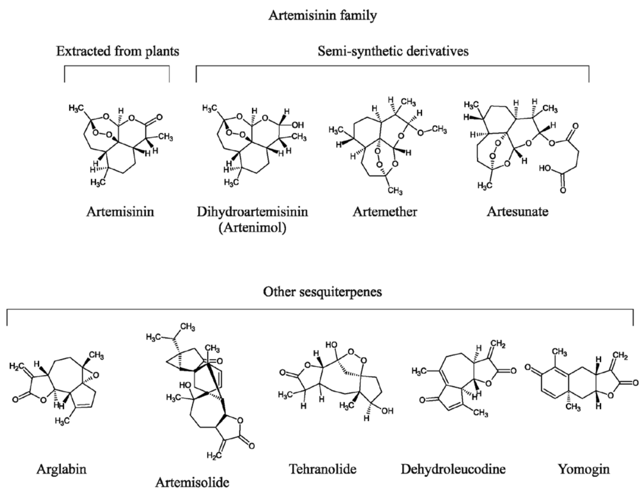

Figure 2 - Molecular structures of artemisinin-family and other Artemisia sesquiterpene lactones (Source: authors)

cells *ex planta* is low. At present, extraction from collected leaves is the only economically viable technology used to produce artemisinin for medicinal purposes. The largest share of the extracted substance goes for further derivatization to produce semi-synthetic derivatives. Artenimol, artesunate and artemether (Figure 2) are the semi-synthetic derivatives of artemisinin developed to increase the pharmaceutical efficacy against malaria. These derivatives are more water-soluble, have higher bioavailability and they reached higher concentrations in plasma when compared to the parental compound artemisinin.

Other Artemisia sesquiterpene lactones are worth mentioning because the pharmacological activity. Arglabin (Figure 2) has an antineoplastic activity and has been proposed in Kazakhstan for the treatment of cancers. One study suggests using anti-inflammatory properties of arglabin to fight the cytokine storm accompanying sever SARS-CoV-2 cases [31]. Artemisolide (Figure 2) also has the anti-inflammatory activity. Tehranolide (Figure 2) has shown antitumor properties [32, 33]. With regard to comparing its chemical structure to other compounds in this review, tehranolide is interesting in that its molecule also contains the endoperoxide bridge similar to that of the artemisinin family. It can be derived knowing the mechanism of action of artemisinins that tehranolide also can be used to treat malaria. The anti-malaria activity of tehranolide had been tested but the published data are scarce. Dehydroleucodine (Figure 2) has the cytotoxic activity killing myeloid leukemia cells [34]. The biological activity of yomogin (Figure 2) is different in that this substance is endowed with a compendium of activities which prevent type-I hypersensitivity reactions (allergy and asthma). Yomogin is an efficient scavenger of biogenic nitric oxide, antagonist of receptors mediating contraction of airways and inhibitor of mast cells degranulation. These properties suggest yomogin as an anti-allergy drug. Table 2 shows lists of Artemisia spp. in which the mentioned compounds are present. No antiviral activity has ever been referenced in published literature for the compounds in this paragraph.

It is worth testing not only *Artemisia spp.* but also representatives from other different genera, species in the large Asteraceae family for the presence of the same compounds or the similar pharmacological activity because various species may contain the same secondary metabolites.

Table 2 - Natural sesquiterpene lactones shown in Figure 1 and Artemisia species in which these compounds are present

	Sesquiterpene lactone					
	Artemisinin	**Arglabin**	**Artemisolide**	**Tehranolide**	**Dehydro-leuc-dine**	**Yomogin**
Species lists [1]	*A.abrotanum*	*A.myriantha*	*A. argyi*	*A.diffusa*	*A.douglasiana*	*A. argyi*
	A.absinthium	*A.obtusiloba*	*A.sylvatica*		*A. feddei*	*A.feddei*
	A. annua				*A. lancea*	*A lancea*
	A. apiacea				*A. myriantha*	*A.montana*
	A.caerulescens				*A. rutifolia*	*A.princeps*
	A. campestris				*A.xanthochroa*	*A.reptans*
	A. carvifolia					*A.vestita*
	A. genipi					
	A. lancea					
	A. tenuisecta					
	A.umbelliformis					
	A. vallesiaca					
	A. verlotiorum					
	A. vulgaris					

Comment: [1] the Pubchem database was used to download lists of plant species for the compounds (sesquiterpene lactones).

For example, artemisinin can be found not only in 14 *Artemisia spp.* but also in *Microliabum polymnioides* and *Tessaria integrifolia*. A brief investigation into of the Pubchem data pertaining to the Asteraceae family shows that predominant secondary metabolites characteristic to Asteraceae are oxygenated terpenoids, phenols, lactones, flavonoids but alkaloids are not present in large amounts.

Artemisinin and derivatives as potential antiviral drugs. Artemisinin has shown the inhibitory effect on the replication of hepatitis C virus [35, 36]. Artemisinin and artesunate were tested against hepatitis B virus and artesunate was tested against human herpesviruses (Table 3). The data from Table 3 are from studies conducted *in vitro*. One clinical report describes treatment of one pediatric patient which received artesunate against foscarnet-resistant and ganciclovir-resistant cytomegalovirus as the last available line of therapy. The treatment with artesunate reduced viral loads which reduction was interpreted as a clinical success. However, no regulatory-approved clinical trials for the artemisinin-family compounds as antivirals have been registered and no results of such trials are present in the published literature. All measurements of the antiviral effect such as effective concentrations for artemisinin-family compounds have come from *in vitro* tests. This field suffers from a lack of results from animal models of viral infections.

Table 3 - Half-maximal effective concentrations of artemisinin-family compounds against viruses

Virus	Compound	Molecular weight of the compound, g/M	EC_{50} [1], uM	EC_{50}, ug/ml
Hepatitis C virus	Artemisinin	282.33	78 uM	22 ug/ml
Hepatitis B virus	Artemisinin	282.33	>100 uM	>28 ug/ml
Hepatitis B virus	Artesunate	384.40	0.5 uM [2]	0.19 ug/ml
Human cytomegalovirus	Artesunate	384.40	3.9 – 6.9 uM	1 – 3 ug/ml
EpsteinBarr virus	Artesunate	384.40	7.2 uM	3 ug/ml

Comments: [1] 50% effective concentration (EC50) is the concentration at which drug reduces a quantitative characteristic of viral replication by half. 2 for hepatitis B virus EC50 was measured by the determining viral DNA in cell culture which is a measure of viral replication.

Artemisia species diversity in Kazakhstan. The region of Central Asia and Kazakhstan has been reported as a centre of the genus Artemisia evolutionary origin and the epicenter of this genus' biodiversity. The Artemisia genus in Kazakhstan is represented by ~80 species. Botanists regret that "endemic and rare species of the genus Artemisia in Kazakhstan are poorly studied" [37] and the authors of this review totally agree with this judgment. Importantly, *A. annua* which is of interest as a possible source of antivirals is endemic to Kazakhstan. The presence of *A. annua* in the local flora does not automatically mean that the local populations contain sufficient artemisinin. Anyhow, the availability of *A. annua* in Kazakhstan requests determining levels of production of artemisinin and other bioactive compounds to assess possibility of using these plant resources for extraction of antivirals. Also, a comprehensive study is necessary to assess the antiviral activity of phytochemicals from Kazakhstan's flora including the activity against SARS-CoV-2.

CONCLUSION

The Artemisia genus is rich in medicinal plants and Kazakhstan's flora is rich in representatives of the Artemisia genus. It is possible to supplement efforts to treat SARS-CoV-2 patients with an Artemisia plant-derived antiviral drug. Existing populations of the plant *A. annua* in Kazakhstan must be studied for the production of artemisinin for which compound the antiviral activity was found. Studies of the antiviral activity of phytochemicals against SARS-CoV-2 and other viruses must be expanded.

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РАСТЕНИЕ ARTEMISIA ANNUA («ПОЛЫНЬ ОДНОЛЕТНЯЯ») ИСТОЧНИК БИОАКТИВНЫХ СОЕДИНЕНИЙ В КАЗАХСТАНЕ, ПОТЕНЦИАЛЬНО ЛЕЧАЩИЙ ИНФЕКЦИЮ SARS-COV-2

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АБСТРАКТ

Род Artemisia («полынь») широко представлен во флоре Казахстана как по видовому разнообразию (не менее 80 видов), так и по биомассе. Представители этого рода, такие как *Artemisia annua* («однолетняя полынь»), привлекают внимание мирового биомедицинского сообщества, потому что эти растения производят необычный сесквитерпеновый лактон артемизинин, который доказал свою эффективность в качестве противомалярийного препарата, а также испытан на противовирусную активность. Из-за своей потенциальной противовирусной активности фитосоединения, полученные из полыни, вызывают интерес в качестве перспективных препаратов против коронавируса SARS-CoV-2, вызвавшего крупнейшую пандемию в XXI веке. В этом обзоре представлено изученное разнообразие вторичных метаболитов, синтезируемых различными видами Artemisia, описывается фактическое практическое значение одного вида *A. annua*, а также возможное использование веществ из этого вида в качестве противовирусных средств. Существует необходимость в дальнейших исследованиях вторичных метаболитов полыни с противовирусными свойствами из-за ожидания продолжения циркуляции вируса SARS-CoV-2 и для того чтобы дополнить арсенал противовирусной терапии.

Ключевые слова: полынь однолетняя; сесквитерпеновый лактон; артемизинин; противовирусная активность; SARS-CoV-2

ARTEMISIA ANNUA («БІР ЖЫЛДЫҚ ЖУСАН») ӨСІМДІГІ ҚАЗАҚСТАНДА ӨСЕДІ ЖӘНЕ SARS-COV-2 ИНФЕКЦИЯСЫН ПОЦЕНЦИАЛДЫҚ ЕМДЕЙТІН БИОАКТИВТІ ҚОСЫЛЫСТАРДЫҢ КӨЗІ БОЛЫП ТАБЫЛАДЫ

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ТҮЙІН

Artemisia («жусан») тұқымдасы Қазақстанның флорасында түр алуандығы (80 түрден кем емес) және биомассасы бойынша кең таралған. Artemisia annua («жылдық жусан») сияқты тұқымның өкілдері әлемдік биомедициналық қоғамдастықтың назарын аударады, өйткені бұл өсімдіктер безгекке қарсы препарат ретінде өзінің тиімділігін дәлелдеген және вирусқа қарсы белсенділікке сыналған ерекше сесквитерпенді лактон артемисинин шығарады. Вирусқа қарсы потенциалды белсенділігіне байланысты жусаннан алынған Фито-қосылыстар XXI ғасырдағы ең үлкен пандемияға себеп болған SARS-CoV-2 коронавирусына қарсы перспективті дәрі ретінде қызығушылық тудырады. Бұл шолуда Artemisia-ның әртүрлі түрлерімен синтезделген қайталама метаболиттердің зерттелген әртүрлілігі ұсынылған, *A. annua*-ның бір түрінің нақты практикалық мәні, сондай-ақ осы түрлерден заттарды вирусқа қарсы агент ретінде қолдану мүмкіндігі сипатталған. SARS-CoV-2 вирусының айналымын жалғастыруды күту және вирусқа қарсы терапияның арсеналын толықтыру үшін вирусқа қарсы қасиеттері бар жусанның қайталама метаболиттерін одан әрі зерттеу қажет.

Түйінді сөздер: бір жылдық жусан; сесквитерпенді лактон; артемизинин; вирусқа қарсы белсенділік; SARS-CoV-2