Ars Pharmaceutica

From Alchemy to Telepharmacy

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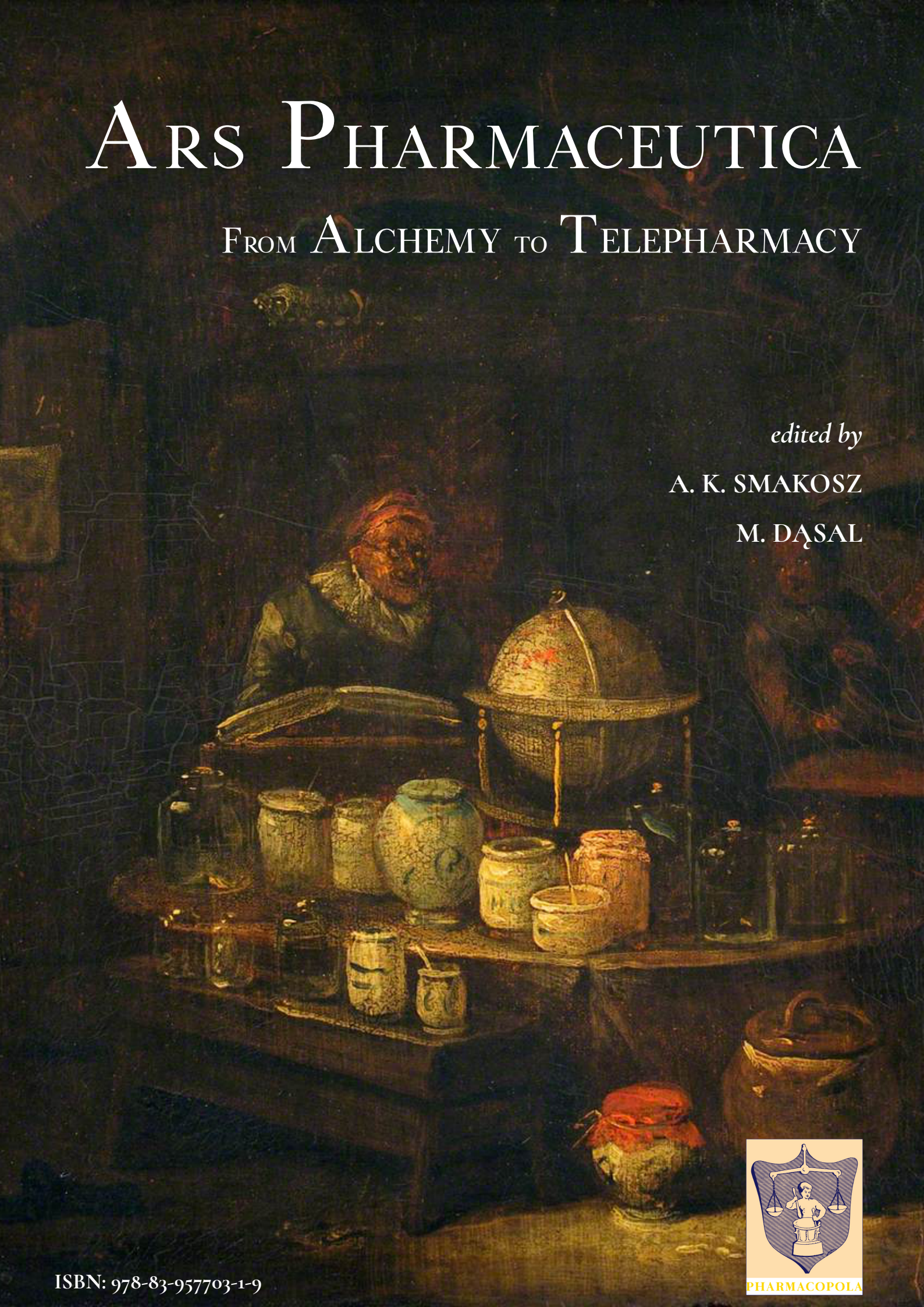

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Book of Abstracs

Edited by

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and

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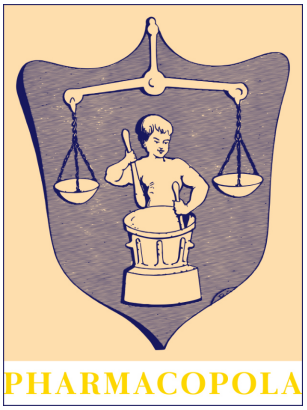

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Abstracts:

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Aspects of disinfectant formulation in the galenic laboratory in the pharmacy

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Phytochemical screening of *Cenostigma microphyllum* (Mart ex G. Don) E. Gagnon & G. P. Lewis (Fabaceae)

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Introduction

Seasonally Dry Tropical Forest and Woodlands (SDTFW) is a global biome of 2,700,000 km² characterized by low annual rainfall (< 1800 mm/year), high seasonality (periods of 5–6 months characterized by less than 100 mm of rainfall) and deciduous, not fire-tolerant vegetation (Pennington et al., 2009; Queiroz et al., 2017). The Caatinga, as integral part of this biome, is the largest dry forest nucleus, with a total area of 849,516 km² and corresponding to 31% of the SDTFW biome in the Neotropical region and it is entirely located in the Brazilian Northeastern region (Pennington et al., 2009; Queiroz et al., 2017).

The SDTFW Caatinga, besides facing multiple anthropic pressures, is also one of the regions most vulnerable to the global climate crisis (Collevatti et al. 2013; Ripple et al. 2019) owing to low rainfall and soil nutrient depreciation (Borchert 1994; Menezes et al. 2012; Buzzard et al. 2015). These two factors that are limiting to the growth and development of plant life, may accelerate the desertification process and affect all biodiversity and ecosystem services (IPCC 2019; Santos et al. 2014; Vieira et al. 2015). However, despite of it, SDTF Caatinga is estimated to be between 5 and 8 thousand plant species, which about 318 of them are endemic, turning it in one of the most privileged as a resource with bioprospective potential that has fundamental importance in pharmacological studies of its flora (Novais et al., 2003; Giulietti et al., 2006).

Furthermore, plants that grow up under scarce climatic conditions may have higher concentrations of natural products compared to individuals of the same species that grow in habitats with wide availability of water (Selmar, 2008). There have been reports about the positive influence of water stress on the concentration of various secondary metabolites, including cyanogenic glycosides,

and catechins (Selmar and Kleinwächter, 2013).

Among the several species present in the *Caatinga*, *Cenostigma microphyllum* (Mart ex. G. Don) E. Gagnon & G. P. Lewis (*Fabaceae*) is an endemic, native and highly abundant species in the SDTFW Caatinga (Fernandes et al., 2019 ; Gagnon et al., 2016), showing considerable importance to the local population, being used for medicinal purposes (in the treatment of digestive diseases, infections and inflammations, due to its antibiofilm and antiprotozoal properties) (Agra et al., 2008; Silva et al., 2020,2014), beyond that it is used as timber and fuel (Gomes et al., 2019). Thus, it is an interesting species to study regarding phytochemical aspect, given local relevance and low availability of information on it in the literature.

Therefore, the objective of this work was to perform the phytochemical screening of hexanic (nonpolar) and hydroalcoholic (polar) extracts, both of leaves and stem barks of the *Cenostigma microphyllum* to verify the presence of secondary plant metabolites with potential use in human health.

Materials and methods

Study site

The study was conduced at the Catimbau National Park, located in the state of Pernambuc—Brazil (8°24'00" and 8°36'35" S; 37°00'30" and 37°01'40" W). The Park is located 281 km from the state capital Recife and covers part of the municipalities of Buíque, Ibimirim and Tupanatinga. Its area comprises approximately 62,300 ha, with a semi-arid climate (Köppen-Geiger Bsh classification), deciduous vegetation typical of hyperxerophytic Caatinga and predominantly lithosols. It presents an average annual temperature of 23 °C and a high variation in its average annual precipitation (480-1,100 mm/year) (Rito et al., 2017) (Fig. 1).

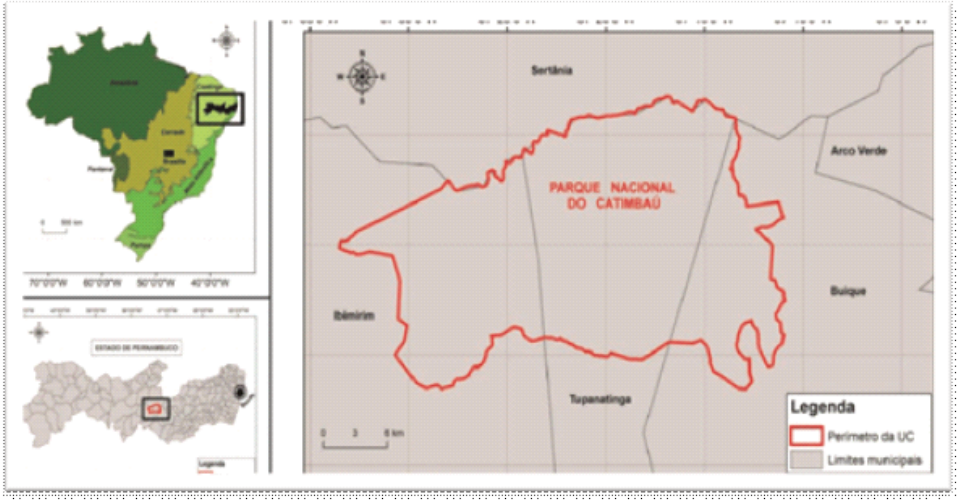

Fig 1. Location of the study plots in the Catimbau National Park, PE—Brazil

Experimental design

The plant material collected consisted of 500 grams of leaves and stem bark of the Cenostigma microphyllum obtained in January 2019 from adult individuals approximately three meters high, which the stem barks samples were removed at one meter over the ground level, while leaves were always mature, without signs of predation and obtained from shaded site on all trees. Then, samples were stored in plastic bags and dehydrated at room temperature (26 ° C) in order to better preserve the phytochemical properties of the material, being subsequently sprayed and sieved before the phytochemical screening process.

Sample collection was authorized by the national Biodiversity Authorization and Information System (SISBIO), registered under number 64367–1. Collection and herbori-zation followed the guidelines as suggested by Mori et al. (1989) with identification performed by Dr. Rita de Cássia Araújo Pereira. Voucher samples were deposited in Dárdano de Andrade-Lima Herbarium, at Instituto Agronômico de Pernambuco (IPA—PE- Brazil) under no. 91695.

Phytochemical screening

Hexanic and hydroalcoholic extracts of the leaves and stem barks were prepared by double maceration technique. In a 50 ml Erlenmeyer flask about ten grams of the pulverized plant material were imerged into 100 ml of hexane PA, keeping under constant agitation for one hour. Then, the crude hexanic extract was filtered and taken to a hot water bath at 110 ºC. Remaining material was re-suspended in hydroalcoholic solvent (70 ml ethyl alcohol PA plus 30 ml distilled water) and followed to the same procedure as descripted previously to obtain the crude hydroalcoholic extract. Subsequently, aliquots of both extracts were removed for phytochemical screening.

Hexanic extracts were tested for presence or absence of saponins, alkaloids, coumarins, volatile oils/terpenoids and simple phenols, while hydroalcoholic extracts were tested for presence of flavonoids (glycosides and aglycone) using the Thin-layer chromatography (TLC) technique, which they were compared to well-known standards as reference model (Tab. 1). Analyzes were carried out applying aliquots of these extracts under silica gel 60 F254 chromatographic plates with aluminum support (20 × 20 cm) (Merck) using capillary tubes (15µL). Then, such plates were eluted in different mobile phases and stains, as suggested by conventional methods (Wagner and Bladt, 1996) and visualized under UV light chamber.

Tab. 1. Secondary metabolite classes, mobile phases, stains and standards used in the phytochemical screening of *Cenostigma microphyllum* (Mart. Ex G. Don) E. Gagnon & G.P. Lewis (*Fabaceae*)

Class	Mobile phase	Stain	Standard
Hexanic extract			
Alkaloids	Precipitation reaction	Dragendorff + HCl 10%	Scopolamine butylbromide (Buscopan© tablets) and *Catharanthus roseus* (*Asteraceae*)
Phenylpropanoids/ Coumarins	Toluene: ethyl ether (1:1 v/v)	Ethanolic KOH 10%	Chloroformic extract of Justicia pectoralis and 1,2-benzopyrone
Saponins	-	Foam test	Aqueous extract of stem bark of *Zizipus joazeiro* (*Rhamnaceae*)
Volatile oils/ terpenoids	Toluene: ethyl acetate(93:7 v/v)	Anisaldehyde-sulphuric acid + heating	Ethanolic extract of *Mesosphaerum suaveolens* (*Lamiaceae*) and *Justicia gendarussa* (*Acanthaceae*)
Simple phenols	Toluene:chloroform: ethanol (40:60:15 v/v)	NP/PEG (NEU)	-
Hydroalcoholic extract			
Flavonoids (glycosides)	Ethyl acetate: formic acid: glacial acetic acid: distilled water (100:11:11:26 v/v)	NP/PEG (NEU)	Quercetin
Flavonoids (aglycones)	Toluene:ethyl ether (1:1 v/v)	NP/PEG (NEU)	Quercetin

Results and discussion

The phytochemical profile of the leaf and stem bark extracts of *C. microphyllum* detected strong presence of phenols, however the presence of flavonoids (glycosides and aglycone) was also observed. On the other hand, the presence of alkaloids, phenylpropanoids/coumarins, saponins and volatile oils / terpenoid was not detected (Table 2).

Tab. 2. Metabolites present in the hexanic and hydroalcoholic extracts of C*enostigma microphyllum* (Mart. Ex G. Don) E. Gagnon & G.P. Lewis (Fabaceae), using the Thin- layer Chromatography (TLC) method

Class	Stem bark	leaves
Hexanic extract		
Alkaloids	-	-
Phenylpropanoids/ Coumarins	-	-
Saponins	-	-
Volatile oils/terpenoids	-	-
Simple phenols	++	++
Hydroalcoholic extract		
Flavonoids (glycosides)	+	+
Flavonoids (aglycones)	+	+

Subtitle: (-) Absent; (+) Present and (++) Strongly present

Many phenolic compounds, terpenoids and phytosterols have been isolated from several species of the *Cenostigma genus* (Zanin et al., 2012). The results observed in *C. microphyllum* are similar to those obtained in the leaves or stem barks of the species Cenostigma pyramidale (Tul.) E. Gagnon & G.P. Lewis, which it is an other widely used medicinal species that it has already possible to isolate phenolic acids (such as gallic acid and derivatives of cinnamic acid) and polyphenols, such as catechins, lignans, flavonoids and derivatives (aglycone, chalcones, catechins, flavonones, flavones and flavonols) (Bahia et al., 2010; Bahia

et al., 2005; Mendes et al., 2000; Monteiro et al., 2005; Saraiva et al., 2012; Silva et al., 2011).

Studies also shows *Cenostigma pyramidale* has metabolites such as condensed tannins, phenylpropanoids, lupeol (a triterpene) and phytosterols (such as β–sitosterol and stigmasterol) (Bahia et al., 2010; Bahia et al., 2005; Mendes et al., 2000; Saraiva et al., 2012; Siqueira et al., 2012), which they were not detected or not tested in the present study. On the other hand, Silva et al. (2020,2014) confirmed the presence of hydrolyzable tannins, terpenoids, phytosterols and amines in the fruits of *Cenostigma microphyllum*. Bueno et al. (2016) observed the presence of hydrolyzable tannins in the stem barks of the Cenostigma pluviosum (DC.) E. Gagnon & G. P. Lewis species, it may also be an indication of the presence of hydrolyzable tannins in the stem bark of this study plant species.

Conclusion

Due to the phytochemical similarities in the composition between *Cenostigma pyramidale* and *Cenostigma pluviosum*, the species *Cenostigma microphyllum* may work as a promising alternative in the treatment of several diseases of traditional populations in the Brazilian semi-arid region, requiring further studies regarding its biological activities, cytotoxicity, mutagenicity and hepatotoxicity.

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Ethnopharmacology of the genus *Taxus*

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"Root of hemlock digged i' th' dark,

Liver of blaspheming Jew,

Gall of goat and slips of yew

Slivered in the moon's eclipse."

(W. Shakespeare, Macbeth, Act 4 Scene 1)

With these words, one of Shakespeare's witches depicted in Macbeth lists the ingredients needed during a magical ritual. The goddess Hecate herself was impressed by the prepared formulation. One of the sources—the yew (*Taxus baccata* L.), famed for its longevity, has been connected for centuries both with world of the dead and immortality. In Celtic culture it was held sacred in pre-Christian times. Simultaneously druids considered described species as the symbol of death and resurrection. Contemporary archaeobotanical records show that T. baccata has been growing in the British Isles for at least 8000 years.

The ancient Greek and Roman authors mentioned yew as a wood used both for bows and as a poison. Theophrastus (Greek philosopher called "father of botany," he lived between 371 and 287 BC) considered the leaves of this plant poisonous to horses. Pliny the Elder (Roman naturalist and encyclopaedist, he lived between 23 and 79 AD) observed, that the "berries" of *T. baccata* are a mortal poison gathered particularly in Spain. Moreover, he was of the opinion, that the word *Toxicon* (lat. poison) was named from this tree. However, it is not so obvious. Some scholars take the view that the name taxus was derived from *taxis* (gr.

arrangement of the leaves like teeth of a comb) or *taxon* (gr. a bow). This is especially interesting because Homer himself wrote about soldiers from Crete equipped with this deadly yew-bows. It is worth pointing out that in ancient times botanical preparations based on yew were used as an abortifacient—often with deadly consequences.

Considering this plant as a link between divine and humankind did not disappear during Christianization of the British Isles. Therefore *T. baccata* was planted around churches and cemeteries. It explains why the old specimens of yew are now rare outside of church grounds.

The name *Taxus* was first proposed for the genus by Tournefort in 1717, and in 1753 this taxon was established by Carl von Linné. In his Species Plantarum he described two species of yew : common yew and Taxus nucifera. The latter is contemporary classified as *Torreya nucifera* (Japanese nutmeg-yew). This *Taxaceae* representative yields edible seeds and cooking oil. It is commonly planted as an ornamental plant. In Japan some esoteric groups are extracting aromatic oil from the crude material (leaves) which is burned by them and used as a meditation agent.

Yew in official medicine

In 19th century yew was not a significant botanical substance, but it was well established in German-language countries. The most common crude drugs obtained from this tree were:

• *Cortex Taxi*—bark

• *Folia Taxi*—leaves (needles)

• *Lignum Taxi*—wood

• *Pseudofructus / Baccae / Fructus Taxi*—the seed cones (strobili)

• *Semen Taxi*—seeds

• *Summitates Taxi*—young shoots

Within the medicines based on yew materia medica the most notable formulations were sirups, tinctures, decoctions, spirits and extracts. Tincture of yew's needles (*Tinctura Taxi*) and extract of yew's needles (*Extractum Taxi*) were mainly used as belladonna (*Atropa belladonna*) substitutes. Botanical preparations based on seeds: Aqua Taxi seminis (yew seeds medicinal water), *Extractum Taxi seminis aethereum* (yew seeds ether extract), *Spiritus Taxi seminis* (yew seeds spirit)

were used in similar manner as a foxglove (*Digitalis spp.*, this plant was used for various heart conditions such as arrhythmia), but without its side effects. It is worth to mention that the seed cones were also used in bronchitis and wood for rabies.

If overdosed, the characteristic symptoms of yew poisoning are: vomiting, dilating pupils, nausea, coma and hallucinations. From ancient times *T. baccata* were known for its poisonous properties. In this case these features are known as cardiotoxicity. All organs of this plant (except fleshy seed cones) contain taxine alkaloids. They cause irregular heartbeat and heart and respiratory failure. Survival after yew poisoning is uncommon.

From traditional medicine to antitumor drug

One of the indigenous people group of North America – Iroquois, used other species from this genus (*T. canadensis* = Canadian yew) in their traditional medicinal system. For respiratory tract infections they prepared a branch decoction. The patient was put in a chair, then he was cooled with a blanket and a steeping, hot liquid was placed under the sick person who was steaming until sweating. For numbness of fingers and legs a decoction of twigs was used. According to Iroquois this crude drug was also helpful against powerlessness.

There is another important yew species from "The New World"—*T. brevifolia* (pacific yew). Certain Native American tribes used the bark and wood for stomach pains and poultice of ground leaves for hard-healing wounds. Decoction of bark was taken as a "blood medicine." In 1960s the National Cancer Institute (US) was screening for American plants with antitumor properties. It came out that the bark extract of Pacific yew stops the growth of several mouse tumours. Furthermore, during the years of research scientists have developed a new antitumor drug for lung, breast and ovarian cancer - paclitaxel. Because of above, most of the original T. brevifolia population ceased to exist (it was converted into a drug). Soon the new methods was developed—e. g. semisynthesis from analogue compound extracted from leaves of our European yew. Contemporary most of paclitaxel is produced via semisynthesis from natural precursor obtained from in vitro culture of common yew needle cells.

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Aspects of disinfectant formulation in the galenic laboratory in the pharmacy

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The current difficult situation, as a result of the Covid-19 pandemic, has caused a demand for something that we took for granted and did not realize that there might be a shortage. However, the deteriorating availability of disinfectants has given us, pharmacists, the opportunity to show the continuing legitimacy of galenical pharmacy and individual preparation of drugs in 21st century. Although disinfectants are now more available than during the "first wave" of COVID-19, it is certainly a good pharmacy business card if it can expand its range with a portfolio that is perceived by the public as "hand-made" and at a more affordable price compared to high prices from commercial manufacturers.

The compilation of recipes requires both basic knowledge of microbiology so that we can reliably determine for which group of microbes the product will be effective and technological knowledge so that we can formulate the product appropriately and thus ensure it´s stability and good applicability. When formulating new prescriptions for disinfectants in a pharmacy, we must be aware of three basic aspects, relating to the following areas:

1. Choice of antimicrobial substance

Alcohols. These hydroxy derivatives of hydrocarbons are used as disinfectants either alone or in combination with other antimicrobials, in which case they also act as vehicles. They act rapidly (at a concentration of 70% within 30 seconds) on a wide range of vegetative bacteria, viruses and microscopic filamentous fungi. The alcohols themselves are sporistatic and have sporicidal effects in combination with selected surfactants or in combination with hydrogen peroxide. They are used in disinfectants in concentrations of 60 - 80% (V / V). The most used e.g. ethanol (*Ethanolum* (*96 per centum*) Ph. Eur. 10), for which the effective concentration optimum is generally considered to be 71%, despite the

variability of the results of experimental work. A more effective alcohol is isopropyl alcohol (*Alcohol isopropylicu*s Ph. Eur. 10), which is used separately e.g. for preoperative skin disinfection in concentrations of 60 - 70%. Isopropyl alcohol at a concentration of 60% shows the same bactericidal activity as 77% ethanol, on the other hand, ethanol is more effective against some types of viruses. In vitro experiments confirmed the efficacy of both isopropyl alcohol and ethanol at the indicated concentrations against SARS-CoV-2 virus. The disadvantage of isopropyl alcohol is, in addition to higher skin irritation, also twice the toxicity (p.o.), compared to ethanol. Alcohols in certain concentrations show technological incompatibility with carbomer (acrylic and polyacrylic acid derivatives, trade name *Carbopol*®) and sodium carboxymethylcellulose (disruption of gel structure to liquefaction). It has been reported in the literature that a maximum of 35% ethanol can be incorporated into carbomer gels without rapid reduction in gel viscosity.

Chlorhexidinium digluconate (*Chlorhexidini digluconatis solutio* Ph. Eur. 10). It is a disinfectant belonging to the group of diguanides. It has a bactericidal effect on gram-positive and gram-negative bacteria and on enveloped forms of viruses. The mechanism of action is disruption of membrane integrity and inactivation of membrane enzymes (at lower concentrations), up to coagulation of the cytoplasm (at higher concentrations). It has the highest bactericide and virucide activity at neutral to slightly alkaline pH, when it occurs as a dication. It is incompatible with anionic surfactants (they can reduce effectiveness). It is used in disinfectants in concentrations of 0.5–4%, possibly in combination with alcohols or quaternary amine salts. A commercially available pharmacopoeial substance is a 20% aqueous solution.

Benzalkonium chloride (*Benzalkonii chloridum* Ph. Eur. 10). This cationic surfactant, which belongs to the quaternary amine salts, is readily soluble in both water and ethanol and can therefore be used in combined disinfectants. Thanks to its surface-active properties, it wets surfaces well, which increases its availability and disinfection effect. The mechanism of action is damage to the integrity of the cytoplasmic membrane of bacteria, subsequent leakage of cytoplasmic components and cessation of metabolism. In vitro experimental work has shown that the antimicrobial is also effective against SARS-CoV-2 virus at a concentration of 0.2% (w / w). Its effective pH optimum lies in the neutral to slightly basic range. In combination with anionic and nonionic substances, mixed micelles are formed and incompatibility occurs. Benzalkonium chloride from 0.1% (w / w) in carbomer bases shows incompatibility (turbidity and flow of the gel) and therefore a different gelling agent must be used in the formulation of the gels.

2. Galenical form of disinfectant.

The least technologically demanding is to formulate disinfection into a solution. The vehicle is most often water, ethanol, isopropyl alcohol or a mixture thereof in a suitable ratio. In the case of crystalline disinfectants, these are simply dissolved in a solvent (e.g. alcohol, which in some cases may potentiate the disinfecting effect of the substance itself). The low viscosity of the solution ensures that the disinfectant active substance reliably gets into all the unevenness of the skin. Gels are a more technologically demanding form. Compared to solutions, they require a certain amount of technological experience to prepare, but especially time, which can be a problem in the current stressful situation in pharmacies. It is also necessary to take into account the possible incompatibilities of the gelling agents with the active ingredients and excipients. If we manage to solve these critical aspects - gels are a more popular form of disinfection compared to solutions. They are well applied to the hands and if we give their composition a certain "upgrade" in the form of humectants, e.g. urea or glycerol (to minimize skin dryness), substances that promote epithelialization and skin regeneration, or odor correction - they can take on the character of a cosmetic product with a specific focus.

Carbomers (*Carbomera*, Ph. Eur. 10; *Carbopol*®) and cellulose derivatives - hydroxyethylcellulose (HEC, hyetellose, Hydroxyethylcellulose Ph. Eur. 10), methylcellulose (MC, Methylcellulosum Ph. Eur. 10), hydroxypropyl-methylcellulose are used as gelling agents. (HPMC, hypromellose, Hydroxy-propylmethylcellulose Ph. Eur. 10). Most of them are commercially available.

The concentration of the gelling agent in the preparation is chosen according to the desired consistency (viscosity) of the preparation and according to which packaging material is intended to be used. When choosing a gelling agent, we are limited primarily by the choice of a suitable effective antimicrobial agent, as we must not allow the possibility of possible incompatibility.

3. Choice of packaging material for the chosen galenical form of the disinfectant

Proper adjustment is no less an important final aspect of product preparation. In addition to protecting the product from external influences, it must provide a convenient and practical application of the disinfectant. The disadvantage of the solution is the impractical application to the hands when using narrow-neck incompressible vials as packaging. This disadvantage can be solved by using a spray applicator on a narrow-necked dark glass vial or by adjusting to a box. However, due to the higher vapor permeability of polyethylene, they are not entirely suitable for long-term storage. Commercially produced disinfectant gels and solutions are often adjusted in PETE (polyethylene terephthalate) packages,

which have improved mechanical properties, are less vapor permeable and have better chemical resistance. In the case of gels, narrow-mouth vials are useful, but a clear attractiveness and improvement of product application can be achieved by using pump vials or plastic extrusion containers. An essential part of the packaging is, of course, the label, which must not lack, inter alia, the qualitative composition of the preparation and the concentration of the active disinfectant.

Examples of recipes suitable for the preparation of disinfectants in the galenical laboratory:

Disinfectant gel with 72% ethanol.

Composition:	894 g (≈ 1,000 ml)
Ethanol 96% (V/V)	667.5 g
Purified water	178.0 g
Glycerol 85% (w/w)	26.7 g
Methylcellulose	17.8 g
Lavandulae aetheroleum	4.0 g

Technological process:

Ethanol 96%, lavender silica, glycerol 85% are weighed into a beaker and mixed. The methylcellulose is then dispersed in the solution. While stirring (preferably using a shaft stirrer), purified water is added and mixed until a clear to slightly opalescent thin gel is formed.

Composition interpretation:

Ethanol at a concentration of 72% (w/w) acts as a disinfectant. Methylcellulose acts as a gelling agent, increasing the viscosity of the preparation. Glycerol is used as a humectant at a concentration of 2.55% (w/w). Purified water acts as a vehicle. It creates an environment for the formation of the gel structure of methylcellulose. Lavender essential oil is a corrective fragrance. However, it can also be theoretically assumed that it "potentiates" the disinfecting effect of the preparation, as most essential oils show antimicrobial activity.

Disinfectant solution with 75% isopropyl alcohol according to WHO (modification of the recipe according to D. Krchňák).

Composition:	843 g (≈ 1,000 ml)
Isopropyl alcohol	591.0 g
Hydrogen peroxide 3% (w w)	41.5 g
Glycerol 85% (w/w)	20.8 g
Purified water	189.7 g
Limonis aetheroleum	gtt X (decem)

Technological process:

Isopropyl alcohol, lemon silica, 3% hydrogen peroxide, purified water and finally glycerol 85% are gradually weighed into the beaker. The solution is stirred until the glycerol is dissolved.

Composition interpretation:

Isopropanol at a concentration of 75% (V/V) acts as a disinfectant. Hydrogen peroxide at a concentration of 0.125% (V/V) acts synergistically with the isopropyl alcohol present as a sporicidal substance, which helps to eliminate possible contamination of the product with spores. The mechanism of action is the oxidative production of free hydroxyl radicals, which have a germicidal effect. Glycerol at a concentration of 1.45% (V/V) acts as a humectant. Purified water acts as a vehicle to dilute isopropyl alcohol to the desired concentration. Lemon oil is a fragrance corrector. However, it can also be theoretically assumed that it "potentiates" the disinfecting effect of the preparation, as most essential oils show antimicrobial activity.

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Ethnopharmacology of *Amanitia muscaria*

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Fly agaric, *Amanita muscaria* is one of the first entheogens known to humankind. It was used by shamans, mostly in Siberia, for ritualistic and recreational purposes. Many scientists look for its presence in folklore in forms of dwarfs or Santa Claus, and also in sacred texts of culture, for instance Indian Vedas. They even try to find in it the genesis of Christianity.

Contrary to the popular opinion, *A. muscaria* is not poisonous, and after having undergone appropriate kitchen processing it can be consumed without risk of psychoactive effects, what has been practised locally through generations in multiple countries such as France, Russia, Japan and the United States. Recreational users of Fly agaric, who still exist today, describe the psychoactive effects of its fruiting body as macropsia, which means disturbances in the perception of size of objects.

Some researchers, in those peculiar hallucinations, seek for the origins of legends about dwarfs or elves, or inspirations for some fragments of Lewis Carroll's "Alice's Adventures in Wonderland." In the areas where Fly agaric was used for shamanic ritualistic purposes, there are regional folklore inspired creams and ointments produced which contain Fly agaric extracts. Those cosmetics are dedicated to various dermatological issues, and they are indicated for alleviating muscle and joint pain.

Modern science uses *A. Muscaria* derivative substances such as ibotenoic acid and muscimol in neuropharmacological examinations in order to cause reversable inactivation of the hippocampus or to get better understanding of the GABAergic system. In in vitro conditions and through tests on rats muscimol's tumour cells inhibiting properties had been found. Scientist also try to find application for this substance in the treatment of epilepsy resist to pharm-

acological treatment and Alzheimer's disease.

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The importance of essential oils in the galenical preparations

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In the recent years, essential oils have begun to gain in importance. They have become a part of the trend of a modern lifestyle based on nature. The human psyche is automatically inclined to prefer drugs that have more pleasant sensory properties compared to conventional drugs. Therefore, essential oils are an ideal candidate for the first adjuvant therapy of diseases, but in less complicated indications they can also be used as *Remedium cardinale*. It cannot be said that essential oils are an absolute novelty—their effects, although not in the form in which they are known to us today, were already known to our ancestors in ancient civilizations. Although they have been widely used and used for medical purposes, their comprehensive complex use can only be selectively mediated today. One such civilization were the Egyptians. Already 4500 years BCE described the therapeutic effects of essential oils in the papyri (the best known is Ebers papyrus), from which we learn that they were used as perfumes, medicines, as part of religious ceremonies and associated with resins for the embalming process. The most commonly used essential oils were from plants as *Commiphora* sp., *Cedrus* sp., *Juniperus* sp., *Coriandrum* sp. and *Origanum* sp.

From a therapeutic point of view, essential oils have been becoming more and more important and useful, especially in the 19th and 20th centuries, when chemical analysis developed rapidly and the chemical composition of essential oils and the context between their structure and effects began to be studied. French chemist and beautician René-Maurice Gattefossé (1881–1950) was the first who used the term aromatherapy—treatment by essential oils that affects human health both physically and mentally.

Essential oils (lat. *Aetherolea*, *Etherolea* or *Olea Aetherea*) are polycomponent mixtures of various nitrogen-free organic substances. From the perspective of consistency they are mainly liquid (rarely solid), transparent, oily substances, in

some cases may have a yellow, green or blue colour. Their specific sensoric property is mostly a pleasant smell. Essential oils are synthesized by plants from primary metabolites to form isoprene units, which gradually condense in the presence of specific enzymes. Their importance for plants is mostly protective—they protect plants from microbial, fungal or animal pathogens.

It is relevant to mention that the reliable use of the effects of essential oils is preceded by their quality. The quality is mainly influenced by three factors: the growing conditions of the mother plant (temperature, temperature, soil, etc.), the storage of the mother plant during transport and the production process of isolating the essential oil from the mother plant. Traditional isolation techniques include steam distillation, pressing or enfleurage (extraction of essential oil from flowers with fat). Supercritical extraction with carbon dioxide is a modern and currently a widely promoted method. Each plant is characterized by a different isolation technique to ensure maximum yield and quality of essential oil.

Today, essential oils are part of basic important pharmacopoeias (eg European Pharmacopoeia) and are used, in addition to mass-produced drugs, also in the pharmacy individual preparation of drug products. According to the literature, essential oils are mainly used as *Remedium corrigens*, but practice shows that they can be used as an effective drug in various indications. Their spasmolytic, diuretic, antiviral, carminative, anxiolytic, antibacterial, epithelial and other effects are most frequent. The chemical composition of the essential oil determines its efficacy and therapeutic group. Dosage forms are mostly in ointments, creams, pastes, gels for external use or solutions, tinctures for internal use. It is stated that essential oils can cause allergic and phototoxic reactions, so their use is limited.

Mint essential oil (*Menthae piperitae aetheroleum*) is used in the preparation of drugs as a topical antiphlogistic, derivatives, antiseptic, antipruginose, mild local anesthetic, internal as an antispasmodic and carminative.

Eucalyptus oil (*Eucalypti aetheroleum*) is used as part of medicines used to treat rheumatism, colds, bronchitis or nasal preparations. Separately it is used for inhalations.

Bitter-fennel fruit oil (*Foeniculi amari fructus aetheroleum*) is used to facilitate coughing up mucus and to reduce cold pressure in the form of oral solutions, syrups or inhalation.

Clove oil (*Caryophylli floris aetheroleum*) is used for mild inflammation of the mouth in case of pharynx to relieve toothache. It is widely used in dentistry as a component of dental preparations (pastes, gels, solutions) because of analgesic effect.

Lavender oil (*Lavandulae aetheroleum*) is used to alleviate the weak effects of mental stress and to induce sleep. It is mainly applied by inhalation. Topically in the form of gels and creams, it is used to heal wounds and burns.

Rosemary oil (*Rosmarini aetheroleum*) is used internally in the form of drops for dyspepsia and mild stomach-intestinal problems. Externally, they are used in the form of ointments, gels and liniment to relieve mild muscle and joint pain.

In addition to the essential oils themselves, components isolated from them are equally important in the preparation of drugs.

Camphor (*Camphora*) is obtained from the wood of the tree *Cinnamomum camphora* L. (*Lauraceae*). It is used externally in the form of solutions, creams and ointments. It has antipruginous, cooling, local anesthetic, antiseptic, hyperemic and derivatizing effects.

Menthol (*Mentholum*) is obtained from the essential oil of the plant *Mentha* × *piperita L.* (Lamiaceae). It has a refrigerant, anti-inflammatory, anti-itchy, local anesthetic, weakly hyperemicizing and derivatizing effect. In particular, ointments, gels and solutions are prepared from it. It is also used as part of throat pain lozenges.

Thymol (*Thymolum*) is obtained from essential oil of Thymus vulgaris L. (Lamiaceae). It has antiseptic, antibacterial and antimycotic effect. Its antiseptic effect is 20 times more effective than phenol, but the advantage is that it does not irritate and corrode the skin.

Historical apothecary recipes

Unguentum emolliens (*Pharmacopoea Hungarica*, 1909)

Rp.	
Cerae albae	20,0
Cetacei	40,0
Olei Sesami	160,0
Olei Rosae	gtt I (unam)
M. f. ung.	

Adspersiorus Chamomilleae

Rp.

Ext. chamomillae fluid	29,0
Olei chamomillae	gtt. V (quinque)
Bolus albae	15,0
Talci	57,0

M. f. plv.

Linimentum saponato-camphoratum (PhBs III)

Rp.

Saponis medicinalis		5,0
Spiritus 95%		80,0
Aquae		7,0
Camphorae		2,0
Olei lavandulae		
Olei rosmarini	aa	0,5
Sol. ammoniae		5,0

M. f. linim.

Kräuter-Haaröl (Diet.)—Herbal hair oil

Rp.

Balsami peruviani		5,0
Olei Bergamottae		3,0
Olei Rosmarini		
Olei Chamomillae		
Olei Serpylli		
Olei Absinthii	aa	gtt. V (quinque)
Cumarini		0,05
Chlorophylli		2,0
Olei Olivae		
Olei Ricini	aa	500,0

M. f. sol.

Currently used magistral formulations

Eucalypti etherolei cremor derivans RDP

Rp.
Eucalypti etherolei 2,5
Levomentholi
Camphorae racem. aa 5,0
Cremoris neoaquasorb ad 100,0
M. f. crm.

Camphorae emulsio cum levomentholo RDP

Rp.
Camphorae racem. 3.0
Levomentholi
Carmellosi natrici. aa 1.0
Polysorbati 80 3.0
Paraffini liquidi 17.2
Aquae purif. ad 100.
M. f. crm.

Globuli oromucosales cum benzocaino

Rp.
† Benzocaini 1.0
Anisi aetherolei
Foeniculi aetherolei.
Menthae pip. aetherol. aa gtt. V (quinque)
Glucosii 5.0
Sacchari 17.0
Acidi citrici 3,0
Aquae purificatae 65,0
Ethanoli 96% 2,0
Gelatinae 12,0
M. f. glob. oromusocal.

Aqua carminativa rubra ČL 1997

Rp.		
Aurantii amari etherolei		
Carvi etherolei		
Caryophylli etherolei		
Cinnamomi etherolei		
Foeniculi etheroleum		
Macidis etherolei		
Mentae piperitae etherolei	aa	0,1
Citronellae etherolei		
Coriandri etherolei	aa	0,5
Citri etherolei		1,0
Ethanolum 96% (V/V)		126,2
Sirupus simplicis		266,0
Ponceau 4R		0,26
Nigrum RN		0,02
Aquae purificatae ad		1333,0
Talci 7,0		

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Women's milk throughout history

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Human milk properties

Human milk, due to its unique and species-specific composition, which fully adapts to the current needs of the baby, is called the "gold standard" in the nutrition of newborns. Breast milk is not only a source of nutrients (proteins, fats, carbohydrates, vitamins, minerals) necessary for proper growth and optimal nutritional status of a newborn, but also provides a number of biologically active compounds, including enzymes, hormones, immunoglobulins, growth factors, cytokines, stem cells. These compounds show direct antimicrobial activity, protecting the immature immune system of a child, and have anti-inflammatory and immunomodulatory properties. Breastfeeding has immediate and long-term health benefits for both mother and baby. Immediate effects for a child include a reduction in the incidence of diarrhea, infectious inflammation of the respiratory tract, necrotizing enterocolitis, bacterial meningitis, and urinary tract infections. In addition, breastfeeding prevents the development of overweight, obesity, type II diabetes, hypertension, and asthma in later life.

Short story of breastfeeding

Human milk has not always been considered as the best food option for a newborn baby. Throughout history, the popularity and perception of breastfeeding has been influenced by many factors, such as the economic, social, scientific and political conditions as well as the current fashion.

In prehistory, breast milk was the only food for a newborns. A milk-based diet was continued until the child was 4–6 years old (the moment of molars teeth appearing). In the Neolithic period, the change from the nomadic to the settled

mode caused that women were forced to spend more time on farming and animal husbandry. The period of breastfeeding has shortened to 2–3 years, and the female food began to be replaced with the first forms of feeders.

In ancient times, breastfeeding was considered as an important and intimate activity. Its significant position is evidenced by many paintings and literature works, where nursing mother represents a symbol of charity, patient and sacrificial love towards another human being. Women often were forced to breastfeed their offspring—they were considered as uniquely adapted and properly endowed to this form of nourishment by the nature. In a situation where the woman was unable to breastfeed, the child was given to wet-nurse. The institution of wet-nurses was particularly successful in Ancient Rome and Greece, where women from the upper classes did not care about breastfeeding. The wet-nurses were carefully selected, and the selection criteria included their beauty, health, quality, quantity and even the smell of milk.

From the "Canon of Medicine" we can learn about the habits regarding infant feeding during the Middle Ages. “Canon of Medicine” was a textbook used in medical schools until the end of the 18th century and was written by the Persian physician and philosopher Avicenna. Breastfeeding was recommended until the child reaches 2 years of age. Then Avicenna urged mothers to slowly and gradually discontinued breastfeeding, while introducing and extending the diet with solid meals at the same time. Children who could not be breastfed were given food in animal horns or wet- mothers were given food.

In the Middle Ages, and then in the modern era, the profession of wet-mothers was the most popular and became a symbol of freedom and luxury. Despite the recommendations of scientists, natural feeding was not favored by prevailing beliefs. For example, following idea of the ancient physician, Soranus of Ephesus, people thought that breastfeeding deprive woman of her beauty and accelerate the aging process. Women willingness for being the hosts was not that strong because breastfeeding was associated with sexual abstinence. It was believed that male sperm had destructive influence on breast milk and could be life-threatening for the baby. Men had the right to use the services of prostitutes while their wives were breastfeeding their children. Women who decided for natural breastfeeding were often harassed by their families and discouraged from breastfeeding by their relatives. During this period, especially in the 19th century, pregnant and lactating women aroused disgust and aversion in society. Women were removed from public life and encouraged to stay at home. Breastfeeding was associated with lactation infertility. The desire of noble-born women was to possess the great number of children, which led to the rapid passing of infants to the wet-mothers. The requirements for wet-mothers became even more strict. In addition to the, the condition of the teeth of the feeder and her character was also considered. The character played the crucial role because people believed

that the baby inherited some of wet-mother features with milk. The poorer social classes used cheaper wet-mother services. Animal milk was given to children as a last resort. People were concerned about inheriting by their children some animal behaviour.

Whenever an economic crisis or financial problems of families appeared, the return to breastfeeding could be always noticed. Usually, it was connected with the loss of a job related with the return to the cheapest form of feeding the baby. The revolution in offspring's feeding took place in the second mid of nineteenth century, the time when the first artificial milk mixture was invented. The formula consisted of cow's milk and grain and was invented by the German chemist Henryk Nestle. Following him, the search for more ingredients that could serve as a substrate for new formulas had started. Unfortunately, the trials had tragic consequences because the child mortality rate increased sixfold at that time. The peak of the formula's popularity was noticed in the 1950s, when the first powder formula was introduced. In the popularization of that form of feeding marketing played a huge role. The commercials stated that feeding babies with formula is much healthier than natural feeding. The effectiveness of this message was confirmed by statistics—the percentage of mothers breastfeeding naturally decreased rapidly. Many myths and superstitions have arisen around breast-feeding, and even today, in the light of strong scientific evidence, breastfeeding remain controversial.

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Ancient pharmacy also solved erectile problems

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Male sexual functions are based on both the hormonal (potentia generandi) and nervous (potentia coeundi) systems. It is a very complex interplay and connection of these two competencies of the biological unit, the result of which are correct physiological functions of the genitals. The second mentioned stimulus evokes mainly psychological and subsequently reflexive tension. It can be declared that the basis of a successful sexual intercourse in men is an erection of good quality, which is controlled by the overall nervous system. From this point of view, it can be divided into two basic sections: spinal and brain.

From ancient times the absence of erection in men was perceived as a kind of loss of masculinity, loss of strength, or of authority of the individual, and therefore medicine has always been trying to correct this delicate but often occurring defect. The term aphrodisios was coined. The word is derived from the name of the Greek goddess of love, Aphrodite. Substances that intensified sexual desire, attractiveness and pleasure were included in the group of aphrodisiacs.

Already in 1744 *Taxa Pharmaceutica Posoniensis* in Chapter XV introduces *Essentiae Aphrodiziaca*—preparations to "stimulate masculinity" (original language —Hungarian: *férfiuságot inditó*). *Benzoes Gummi* was used for this purpose. Essential oils were also relatively widespread, which were supposed to solve erectile problems both systematically and locally. For example, the success of the internal use of Salvia sclarea essential oil was based on observations that an individual receiving long-term treatment could have reached a calmer state. It is well known that an erection in a state of neurosis—usually—is not sufficient. The success probably lay in the anxiolytic effects of the constituents (aldehydes, thujones, geraniol, ketones, etc.).

Cinnamon Ceylon (*Cinnamomum zeylanicum* Blume), for example, was used in French medicine as a sexual stimulant with a local effect. The physiological principle of its operation is in the presence of irritating substances, causing local irritation at the site of application and its congestion (cinnamic acid, cinnamon alcohol and the like).

The last form of administering essential oils for the above purpose is inhalation, i. e. *via* the respiratory entry. The most famous preparation is undoubtedly essential oil with the scent of the Ylang ylang plant (*Cananga odorata* Hook. f. & Thomson). This essential oil contains sesquiterpenes. It is their effects that can be attributed to the effects leading to reassurance.

More current medicine also brought about such preparations, the use of which bordered with toxicological risks. One of such examples is a preparation made of plant *Pausinystalia yohimbe* Schum. called *Yohimbinum hydrochloricum*. It is an alkaloid from the bark of a plant. A substance that dissolves well in water causes genital irritation by dilating blood vessels and activating spinal reflex centers. A known experiment in a male cat at a dose of 0.2 mg/kg intravenously induced an erection leading to ejaculation. In common practice, 0.003 to 0.03 g of p. dose to 0.10 g p. the. The effect was shown after two weeks. Nausea and spasms were observed at high doses.

A really exceptional preparation was a powder made of *Lytta vesicatoria* L. The body of this green beetle contains the venom cantharidin, which is nephrotoxic. How does the golden-green fine powder prepared from the dried bodies of an erection beetle relate to an erection? Systematically and toxicologically. The lethal dose for an adult is in the range of 2–3 grams of powder. When administered orally, there is a state of general intoxication, salivation with inconsolable thirst, burning of the pharynx, vomiting with admixture of blood, dhiarrea and subsequent inflammatory processes. These cause intense blood flow to the bladder and genitals and, at higher doses, painful long-term erections. After a few days, the exposed person dies due to anuria and uraemia. It is clear that the use of this preparation has been extremely risky and often accompanied by irreversible consequences.

A very rare situation is when erection is to be considered a potential negative side effect of a galenic preparation . The venereal tea mixture for the treatment of gonorrhea (*Gonorrhoea*), containing *Herba herniariae* and *Uvae ursi herba*, must not be drunk in the evening. The patient should lie down with an empty bladder to avoid a painful and contraindicated erection at night. Heroin, for example, was used in the past to eliminate or deal with this side effect of a painful erection.

I conclude with ancient method of treating erectile dysfunction with a prescription containing a plant extract that was rediscovered in the late 1990s.

Liquid extract from the root of echinacea (*Echinacea angustifolia* DC) is an aphrodisiac when used internally, in a dose of 0.30–3.00 g in a glass of water. In combination with Hamamel virginian extract, it was also used as an anti-hemorrhoid with application directly to the rectum.

Rp.

Extracti echinaceae angustifoliae fluidi	30,00
Extracti hamamelidis virgíniae fluidi	60,00
Aquae destillatae	30,00

Erection, or rather its quality and its duration has a significant effect on a man's mental state and therefore this dysfunction has been addressed since ancient times. From the point of view of modern pharmacotherapy, a large part of treatment currently proves to be absurd or inadequately risky. What has not changed at all—from the point of view of the medical/medicinal approach—is the effort to correct the adverse consequences, the possible occurrence of erectile dysfunction and also the correction of the very problem.

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History of beta-blockers drug class

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The author focuses on recalling the history of creation of beta-blockers, starting from the scientific works on these preparations by Raymond Ahlquist. The research of this scientist, originally looking for the cure for disorders of menstrual cycle, initiated the discovery of the effect of sympathomimetic amines on adrenotropic receptors. It resulted in the publication in 1948 of a work entitled "Research on adrenotropic receptors" which is considered to be a milestone in modern pharmacology.

Next he refers to the first beta-blocker presented in the medical journal Lancet in 1964 which is soon to be introduced into clinical practice – propranolol. Taking into consideration the time passing, nearly 60 years have passed since that time – the author emphasizes the initial use and the increasing importance of beta-blockers in a modern clinical practice. Representatives of the group of these drugs are used in the treatment of hypertension, congestive heart failure and some types of arrhythmias.

Lactoperoxidase as a new molecular target in infectious oral diseases

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Lactoperoxidase (LPO) is a heme glikoprotein secreted, among others, into saliva, tears, respiratory tract and gastrointestinal mucus etc. This enzyme together with its (pseudo)halogenation cycle substrates—H_2O_2 and thiocyanate ions oxidized to hypothiocyanite ions, forms one of the main systems involved in antimicrobial defence within the oral cavity (Thomas & Aune, 1978; Magacz et al., 2019). Its antimicrobial action is based on oxidation of microorganisms thiol moieties of proteins leading to loss of their biological function (Bafort et al., 2014).

In bacterial and inflammatory diseases such as dental caries or periodontitis, as a result of extensive H_2O_2 production (oxidative stress) by host and microbial oxidases, lactoperoxidase active center is oxidized to a less reactive intermediate known as Compound II (viz. the oxo-iron(IV) intermediate of LPO) resulting in decreased generation of antimicrobial products. Compound II is a relatively stable form without the ability of hypothiocyanite synthesis (Gau et al., 2016). Moreover, this form when not reduced to native form could be oxidated to Compound III ultimately irreversibly losing its biological activity. Compound II could be reduced to the active native form by means of the reaction with broad spectrum of phenolic compounds of endogenous (proteins) and exogenous (xenobiontics, food, drugs) origin (Gau et al., 2018).

In presented research *Reynoutria* sp. rhizome extracts, due to their high polyphenol content, have been tested as potential source of compounds able to reactivate the antimicrobial activity of lactoperoxidase through converting the Compound II intermediate to native LPO state (FeIII(P)LPO). In our study, 70% acetone extracts of *Reynoutria japonica*, *Reynoutria sachalinensis* and *Reynoutria* × *bohemica* together with their five fractions (butanol, ethyl acetate, ethyl ether, dichloromethane and water residue) and four selected polyphenols dominating

in the studied extracts, were tested towards lactoperoxidase reactivating potential.

For this purpose, IC50, EC50 and activation percentage of hypothiocyanite synthesis was determined spectrophotometrically by Ellman's method. Furthermore, to evaluate the mechanism of reactivation, the rate constants for the conversion of Compound I (*viz.* the oxo-iron(IV) porphyrin π–cation radical intermediate of LPO) to Compound II and Compound II to FeIII(P)LPO in the presence of extracts, extracts fractions and selected polyphenols have been determined using direct stopped-flow spectroscopy. Finally, the ability to enhance the antimicrobial properties of the lactoperoxidase system was tested against *Streptococcus mutans* using direct optical density measurements of bacterial cultures.

We proved that *Reynoutria* sp. rhizome is the source of lactoperoxidase peroxidation cycle substrates which can act as both activators and inhibitors of the antimicrobial properties of that system. Concentration of tested extract/fraction or compound was the deciding factor of observed effect. In lower concentrations activation of hypothiocyanite synthesis was observed nevertheless increase of concentration led to complete inhibition of lactoperoxidase (pseudo)halogenation cycle reaction. Presented study shows that the reactivation of lactoperoxidase by some phenolic compounds could become a potential therapeutic target in prevention and treatment support in some infectious inflammatory oral diseases.

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The genus *Anthemis*—medicinal use of a nonmedicinal plant

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Chamomile (*Matricaria recutita* L.) is one of the most widely used and well-documented medicinal plants in the world and it is included in the pharmacopoeia of 26 countries. It is used primarily as a sedative, anxiolytic and antispasmodic as well as a treatment for mild skin irritation and inflammation.

The genus Matricaria comprises approximately 130 species, primarily Mediterranean flowers, although some species can be found in southwest Asia and South Africa. Matricaria recutita L. is a herbaceous plant indigenous to Europe and western Asia. Nowadays, it is mainly cultivated in Europe, South America, and, to a lesser extent, in Africa.

In Bulgaria it is a preference to collect your own herbs. But it is thought that there are two types of chamomile – the medicinal one (genus *Matricaria*) and the nonmedicinal (genus *Anthemis*). The two plants are from the same family (*Asteraceae*) and look very similar, but the natives may differ the two kinds and collect only the "medicinal" one and avoid the other. But in recent years the presence of phenolic compounds in species of the genus Anthemis has been established which determine its antioxidant effect and its therapeutic application which may be used to treat different medical conditions.

Chamomile is used both internally and externally to treat an extensive list of conditions. It is used externally for wounds, ulcers, eczema, gout, skin irritations, neuralgia, sciatica, rheumatic pain, hemorrhoids, mastitis, and leg ulcers. Chamomile is also extensively consumed as a tea or tonic. It is used internally to treat anxiety, hysteria, nightmares, insomnia and other sleep problems, convulsions and even delirium tremens. One of chamomile's main roles is as a multipurpose digestive aid to treat gastrointestinal disturbances including flatulence, indigestion, diarrhea, anorexia, motion sickness, nausea, and vomiting. Chamo-

mile is thought to heal ulcers and act as an herbal bitter to stimulate the liver.

Main active constituents are chamazulene, apigenin, and bisabolol. Chamomile's essential oil comprises 0.5% to 1.5% of the flower head. One hundred twenty chemical constituents have been identified in chamomile including terpenoids, flavonoids and coumarins. The essential oil of chamomile is a light blue color due to the terpenoid chamazulene. Chamazulene is an artifact formed during heating and comprises about 5% of the essential oil. It has anti-inflammatory, antiallergic and antispasmodic properties. Bisabolol is a spasmolytic for intestinal smooth muscle. It also has anti-inflammatory, antibacterial, antipyretic, ulcer-protective and antifungal properties. The flavonoids apigenin and luteolin possess anti-inflammatory, carminative, and antispasmodic properties. Apigenin binds to GABA receptors and has a mild sedative effect. The coumarin umbelliferone is reported to be antispasmodic, antibacterial, and antifungal.

In 2019, scientists from the Faculty of sciences at University Badji-Mokhtar, Annaba, did a study designed to determine a phenolic profile, antioxidant, and antibacterial potential of (dichloromethane, ethyl acetate, n-butanol and aqueous) fractions obtained from the aerial parts of plants from the genus Anthemis. Spectrophotometric and RP-HPLC analyses were carried out to determine the phenolic profile of each fraction. Antioxidant activity was determined by diphenyl 2–pycril hydrazil (DPPH), 2, 2′–azino–bis 3–ethylbenzthiazoline–6–sulfonic acid (ABTS), and β-carotene linoleate bleaching (BCB) assays. Antibacterial activity was determined by the agar diffusion method. The results showed that ethyl acetate fraction contained the highest number of phenolic compounds. Naringin (68,7 ± 16,8 µg/mg), tannic acid (47,64 ± 4,2 µg/mg), and quercetin (44,80 ± 2,2 µg/mg) were found as the major phenolic compounds as judged by RP-HPLC. Also, ethyl acetate fraction exhibited the highest antioxidant activity in DPPH and ABTS assays with an IC50 value of 0,11 and 0,56 mg/mL respectively, while the butanolic fraction demonstrated the highest antioxidant activity in BCB assay (PI = 58,65%). In addition, ethyl acetate fraction showed promising antibacterial activity, with good efficiency against Gram bacteria. Staphylococcus aureus (19 mm at 10 mg/disk) was found as the most sensitive bacteria.

Another study from the Sapienza University of Rome, Italy done with Anthemis cretica subsp. petraea (Ten.) extracts proofed the presence of parthenolide, 9α–acetoxyparthenolide, tamarixetin, 7–hydroxycoumarin, 4′–hydroxyacetophenone, leucanthemitol, and proto-quercitol. Isolation of the compounds was achieved by using column chromatography while their identification was achieved through spectroscopic and spectrometric techniques. The presence of these compounds is of great relevance. Parthenolide and 9–α–acetoxyparthenolide are chemosystematic markers of the family, thus confirming the correct botanical classification of the species. Conversely, compounds tamarixen,

4'-hydroxyacetophenone and proto-quercitol were identified for the first time in the species and, instead, confirm the tendency of endemic entities to develop characteristic metabolite patterns in respect to cosmopolite species. Moreover, the presence of compounds leucanthemitol and proto-quercitol has ecologic implications and may be linked to this taxon's adaption to dry environments. From a medicinal standpoint, the isolated compounds are endowed with interesting biological activities (antioxidant, neuroprotective, antiinflammatory, antileukemic, proapoptotic, and antidiabetic).

The two studies presented, as well as many others, refute the Bulgarian traditional notions of the nonmedicinal use of the genus Anthemis and prove that extracts from it can be used to treat many medical diseases and conditions.

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Modern synthesis of polymers used in pharmacy

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Among many classes of substances employed in obtaining pharmaceutical formulations, polymers are important excipients. In contrast to small-molecule compounds polymers have many specific properties e.g. mass of polymer macromolecules is not fixed value and vary depending on the degree of polymerization i.e. amount of repeating fragments building polymer's chain. Properties such as monomers' order or degree of polymerization can vary depending on the way of synthesis. Properties of polymer impact the polymer's physical and chemical parameters that can further determine the application of the obtained macromolecular compound.

Polymer synthesis methods have evolved from simple hard-to-control methods to more complex and designable methods, giving more control over synthesized macromolecules properties. In the present work, some modern, innovative methods of polymer synthesis utilized in pharmaceutical applications will be presented. One example is ring opening polymerization employed in obtaining polymers out of ring-present monomers. This strategy can give us some advantages like more control over the process. The reformation of the monomer's ring into a linear polymer chain is one of the driving forces in the process of ring opening polymerization, which could result in less drastic conditions of the process and better outcomes.

Many other techniques are used depending on desired properties and application. Bulk, solution, suspension, precipitation, emulsion, biopolymerization techniques can be applied in the synthesis of desired material for pharmaceutical application. Some of them are presented in work.