REVIEW OF HERBAL MEDICINE AS A NATURAL GIFT AND PROPER RIFLE TO OVERCOME PATHOGENIC INFECTIONS

Mohammad Ali Shariatim,*, Elena Zakabunina2, Vladimir Ermolaev3, Alexey Ilushkin4, Ekaterina Sepiashvili5, Vera Simonova6, Sergey Okhrumenko7, Lilya Ponomareva7, Natalia Bratishko7, Ruslan Maksayutov7, Elena Melnikova7, Viktor Konovalov7, Viktor Klimov8, Godswill Ntombi Ntsefung9

Address(es):
1K.G. Razumovsky Moscow State University of technologies and management (the First Cossack University), Moscow, Russia.
2Russian State Agrarian Correspondence University143907, Moscow region, Balashikha, Russian Federation.
3T.F. Gorbachev Kuzbass State Technical University, Kemerovo, Russian Federation.
4Department of Plant Biology, Faculty of Science, University of Yaounde 1, Cameroon.

*Corresponding author: shariatymohammadali@mail.com

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ABSTRACT
Plants are used for several purposes in different industries like pharmacy, food, cosmetic etc. Some of them like spices have antimicrobial and antioxidant properties due to their capacity to produce secondary metabolites. In recent decade, the emergence of novel diseases, epidemics, and even pandemics along with the ability of a large group of pathogens to adapt against available antibiotics have caused scientists to explore natural and new sources of antimicrobial agents. These natural antimicrobial compounds are broadly used to design innovative drugs, in particular for those pathogenic strains that have been resistant to existing antibiotics in market. This review represents some of the recent findings on the antimicrobial activities of medicinal herbs.

INTRODUCTION
The use of herbal drugs to treat a large number of diseases could be traced back to over 5 thousand years. Mankind started to explore components with acceptable therapeutic potentials as soon as they began to identify them (Nweze et al., 2004; Vineela and Elizabeth, 2005; Pavithra et al., 2010; Shinwari and Qaisar, 2011; Shakya and Shukla, 2011; Aizoreky and Nakahara, 2003; Clementi et al., 2014; Zaheer et al., 2021; Sultana et al., 2021; Khouchala et al., 2021).

The term “medicinal herbs” refers to not only those used as sedative agents but also those that could be incorporated as flavors, drinks, sweeteners, natural pigments, herbicides as well as cosmetic products (Oni, 2010, 2017). Medicinal herbs are composed of adapted antimicrobial systems through production of secondary metabolites in their cells (Kim et al., 1995; Ahmad and Beg, 2001; Alagesabaopathi, 2011).

In folklore medicine, herbal drugs are used to mitigate the risks of pathogenic infections. Awareness of side effects involved in the application of chemical drugs might shift people’s interest towards more natural products to avoid such health issues. Beside side-effects, the incidence of multi resistant pathogenic strains to available antibiotics is considered to be another driving force towards finding a proper candidate to overcome resistant strains.

Developments in chemical sciences and the discovery of complicated synthetic organic systems have led to the outreach of pharmacology. On the basis of WHO report, it is estimated that 80 percent of population worldwide are positive towards medicinal herbs and conventional medication methods applied by folk healers. Plants used in such cases contain different constituents that allow them to be used as a part of food supplements, phyto-pharmaceuticals, novel drugs and many more (Farnsworth and Lou, 1983; Hammer et al., 1999; Mukherjee, 2002; Janovska et al., 2003; Bodeker et al., 2005; Ahmed et al., 2020).

From the economical viewpoint, plants are considered to be a proper revenue source due to their biologically active secondary metabolites such as phenolic compounds with different phyto-pharmaceutical activities (Stary and Hans, 1998). It is almost popularized the empirical application of medicinal plants and most countries have organized their facilities to contribute in screening programs of medicinal plants in order to explore and stabilize their antimicrobial activities in primary health care (Baba-mousa et al., 1999).

Like most organisms, medicinal herbs are influenced by environmental conditions that cause changes in appearance, flower, leaves, fruits, and in particular natural composition profiles which can even alter the antimicrobial activities (Balandrin et al., 1985).

With no doubt, antibiotics are one of the most leading discoveries achieved in the 20th century. Nevertheless, less than half of infectious diseases are being medicated using them (Preethi et al., 2010; Sharma, 2011). This might arise from the consecutive years of pathogenic outbreaks and their widespread along with successive and misuse of antibiotics. Therefore, the incidence of multi-drug resistant pathogenic strains shifting towards a global therapeutic issue (Dean and Burchard, 1996; Enne et al., 2001; Westh et al., 2004).

One major challenge that scientists face is how to control drug resistant pathogenic strains with less vulnerability to antibiotics. This has led to the exploration of innovative drug sources with lower side effects and reduction of
adulteration (Silver, 1993; Sieradzki et al., 1999; Debasis, 2014). This review aims at presenting a perspective on previous and recently findings on the application of medicinal herbs to overcome infections caused by pathogens as a contribution towards introducing herbal drugs as an innovative solution to mitigate the incidence of resistant pathogenic strains.

**Bioactive components derived from medicinal herbs**

One characteristic discriminating plants as medicinal herbs is the metabolic mechanisms of secondary metabolite production as final products that can be applied to treat various maladies. Some of the natural secondary metabolites in medicinal herbs are presented in the next section.

**Alkaloids**

Alkaloids are defined as chemical compounds with at least one nitrogen atom in a heterocyclic ring. Biologically, alkaloids are nitrogen compounds produced through synthetic methods or found in naturally occurring forms in plants or animals. Most alkaloids are crystalized components which could combine with acids and produce mineral salts. These components are explored either in free form, salts or N-oxides and mostly accumulated in storage tissues including roots, stems, flowers, seeds and active photosynthetic tissues. The production rate of alkaloids wane as the end of autumn approaches. The amount of alkaloids constitutes 10 percent of dry weight of epidermal tissues like cocaine, colchicine, as well as sterooidal alkaloids like nicotine. The stated alkaloids are considered to be the first plant defending system. The structure of alkaloids varies with respect to the synthesizing and accumulation location, the stage of growth, their life cycles, as well as plant sections. After addition of sodium bicarbonate or ammonium, alkaloids would be precipitated and extracted using organic solvents (Torras-Claveria et al., 2014). Up to now, more than 5000 alkaloids have been detected in different parts of plants like pomegranate root, poppy capsule, datura leaves, and cannabis fruit. Interestingly, alkaloids have effects on nerve system and have sedative properties. They also have anti-cancer activities, stimulating impact like caffeine in coffee, and anti-parasite activity like alkaloids present in pomegranate root (Torras-Claveria et al., 2014). Figure 1 depicts some of the alkaloids.

![Figure 1 Selected alkaloids in medicinal herbs](image)

**Flavonoids**

Flavonoids are plant-based compounds with heart healing properties. The term “flavonoids” represents a large group of phenolic compounds that are derived from phenyl propanoid with a Fifteen-Carbone atom structure. These compounds carry out various functions in plants such as plant pigmentation and UV filtration in plants. They could also perform some functions in the human health care system; increasing antimicrobial strength, mitigating oxidation through chelating ions such as iron and copper, controlling cancer cells within gene expression, improving immune system, playing anti-viral, anti-inflammation, anti-allergic, and anti-mutation and even anti-hepatitis roles in the body (Kumar and Pandy, 2013).

**Glycosides**

Glycosides are secondary metabolites composed of a simple sugar like glucose which is linked to another functional compound by means of glycosidic bond. Glycoside are classified on the basis of glycone type, type of glycosidic bond as well as glycone.

**Bitter compounds**

Pharmacologically, bitter components are related to terpenic group which leads to the release of azoelene and other glycosides with different chemical structures (Aliani and Eskin, 2017).

**Terpenes**

Terpenes, the main constituents of essential oils, are built of carbohydrate. Some of the terpenes contain oxygen included components like alcohol, aldehyde or ketones, but are still categorized as terpenes. Various classifications of terpenes are as below (Breitmaier and Eberhard, 2006):

- Hemi-terpene: They are made of a unit of isoprene. Isoprene is considered merely to be a hemiterpene. However, some of the hemi-terpenes include oxygen like isovaleric acid.
- Mono-terpene: composed of two units of isoprene. One of the alcoholic monoterpenes is geranyl. - Sesquiterpene: contains 3 units of isoprene like furanols.
- Diterpene: made of 4 units of isoprene and are derived from geranyl pyrophosphate.
- Sesterpene: made of 5 isoprene.
- Triterpene: made of 6 units of isoprene. Squalene, the main part of isoprene of shark liver oil, is a member of this group.
- Tetramerpenes: made of 8 units of isoprene such as no ring Lycopene
- Poly-terpene: made of a long chain of isoprene like natural rubber.

**Essential Oils**

Essential oils are recognized as liquid components at ambient temperature, solid at cold temperatures, and soluble in organic solvents like chloroform, acetone (Reddy, 2019). They contain different micro-constituents (Figure 2).

![Figure 2 Selected micro-constituents that are presented in essential oils](image)

**Antimicrobial properties of essences**

Since essential oils have hydrophobic properties, they could easily diffuse in lipid membranes of bacteria or mitochondria, resulting in interference of efflux pump mechanism which causes the leakage of vital molecules and ions from bacteria,
ultimately leading to death (Cox et al., 2000). The same mechanisms also lead to death of fungi cells (Ulte and Smid, 2000). The position of hydroyx group in essence determines how much antimicrobial activity might a compound depict. (Dorman and Deas, 2000).

Effective factors on antimicrobial activities of essential oils

There are several factor affecting antimicrobial activity of essential oils; they are categorized into 2 groups, internal or intrinsic properties of food such as structure, water content, protein, carbohydrate, salt and pH, and external factors including temperature, light, atmosphere and type of packaging (Tassou et al., 1995). Essential oils portray hydrophobicity which allow them to partition into membranes and therefore increase antimicrobial activity. Unlike fat and protein, carbohydrates have no protecting efficacy on bacteria (Melholm and Dalgaard, 2002). Physical structure of food has significant effect on antimicrobial activity. Thus essential oils are more effective against pathogens in liquid food media such as milk, compared to solid structures like meat (Skandanis et al., 2000).

Mechanisms of action

Antimicrobial activity of extracted compounds has been evaluated individually in laboratories. However, the obtained results from various studies have been contradictory and this makes their comparing and judgement effortful (Mann and Makham, 1998; Manou et al., 1998; Skandanis et al., 2001). Besides, it is not still clarified whether the applied methods are targeting to evaluate antimicrobial activity and/or to mitigate the microbial growth. Antimicrobial assessments measure the diameter of inhibited growth area around inoculated paper-discs with an antimicrobial compound on agar considering the following: inhibition of bacterial growth on agar surface with diffused antimicrobial components; and minimum inhibition concentration of antimicrobial activity in liquid environment.

In addition, three important factors which might influence the results of experiments are:
- the combination of parameters in regard to test samples;
- the type of microorganisms and their growth conditions;
- the applied methods in counting of live bacteria.

Most studies like diffusion disc or turbidimetry are on the basis of growth inhibition. The uniform distribution of essential oils in agar is of great importance. Besides uniformity, the present of bioactive compounds are also effective on the results; in lower concentrations, bioactive compounds could act in antagonistic or synergistic manner.

Diversity in the antimicrobial reactions of the components arise from their simple form or their use in combination with complexes (Stechini et al., 1993, 1998). Considering the type of reaction, various determination methods are used. Turbidity is a non-destructive and inexpensive method but has low sensitivity. This method could help with determination of upper section of growth curve; therefore, to correlate the results with the counting of live cells in agar, the method needs to be calibrated.

Changes in absorbance manifest the only response when the total count is 106-107 CFU/ml. The physiological conditions of cells (intact or destroyed), and oxidation level of essential oils could be effective on the absorbance level. Determination of antimicrobial activity is based on monitoring of microbial metabolism. Impendence techniques are employed to screen destroying activities and to assess growth kinetics in mathematical models (Lachowicz et al., 1998).

Conventional techniques depend on the number of live cells counted in plates. However, such techniques are time-consuming and require high-costs. Minimum inhibition concentration (MIC) is determined through consecutive dilution of broth by plate count (Lambert and Pearson, 2000). This requires increasing the monitoring of compounds and microorganisms (Lambert and Pearson, 2000). It could favor simultaneous evaluation of single or several preservatives, and consequently determination of MIC based on mathematical models.

Food applications

Microorganisms are considered to be one of the oldest and successful creatures in our planet, due to their high adapting and survival potentials compared to other organisms that are annihilated after a while. Subjecting pathogenic microbes to antibiotics produced from other microorganisms (the latter introduced as probiotics) could lead to the development of resistant mechanism; therefore, it is not surprising that mankind encourages the ever growing problematic challenges in regards to the control of microbes (Opal et al., 2008).

It is estimated that 10-20 percent of plant population could be used as drugs to serve health care processes like isolation, purification and extraction of herbal drugs which may lead to the production of a group of components with biological activities (Naczk and Shahidi, 2006; Kilwhage et al., 2006).

Among the extracted components, some of them like essential oils have antimicrobial activity. In-vivo techniques are used to evaluate antimicrobial activities of essential oils (Nychas and Tassou, 2000). Some of the ambient conditions are also critical for the efficacy of antimicrobial lethality like the presence of oxygen. For instance, Paster and coworkers found that essential oil of thyme is active against S. aureus and S. entrididis in aerobic and anaerobic conditions (Paster et al., 1990). In addition, essential oil of oregano was more effective in the presence of 41% CO2, 31% oxygen, and 28% nitrogen compared to atmosphere. In another study, essential oil of thyme was shown to have antimicrobial activity against S. aureus and S. entrididis at modified atmosphere packaging at 1°C, and S. putrefacins and P. phosphurum in treated cod fish with essential oil of oregano (Tassou, 2002).

Esential oils are mostly combined with protein, fat, salt and sugar, therefore only limited results about the concentration of essential oil (EO) which remains free could exhibit antimicrobial activity. External factors like temperature limit antimicrobial activity of EO (Davidson, 1997). Physiological properties of bacteria grown in food matrices differ remarkably from those grown in different liquid cultures. Such differences could be due to the following reasons: population, availability of nutrients, availability of oxygen, and the accumulation in final products.

Mechanism of action

The mechanism of action of essential oils depends on the concentration (Prindle and Wright, 1977). Lower concentrations prevent energy related enzymes while higher amounts cause precipitation of proteins. Nonetheless, it is still under question whether the damage to membranes are associated with the amount of antimicrobial compounds contacting the cell membrane or their effects on cells injury leading to cell death. Solutions of trace elements like iron have negative effects on essential oils. Hence, one proper way to inhibit microbial growth might be limitation of cell availability to such ions like iron. Furthermore, ferrous iron could combine with phenolic compounds and indirectly lead to cell destruction owing to oxidative stress (Friedman and smith, 1984). Aldehyde groups in some animal and plant tissues react with main base and prevent biosynthesis of the cell wall (Patte, 1996). Phenolic compounds, essential oils and phytoalexin are mostly active to inhibit microbial growth, rather than exhibition of toxic effects (Tokutake et al., 1992). Leakage of cell membrane might not directly influence microbial growth but moderate the metabolic processes of microorganism (Kubo et al., 1985). Behavior of essential oils in destroying gram positive or gram negative bacterial could be considered as another critical reason.

Compared to gram negative bacteria, gram positive ones are more sensitive (Dabbab et al., 1970; Shelef et al., 1980, 1983; Farag et al., 1989). However, such inhibition mechanisms could be found among gram negative bacteria. For instance, E. coli is more resistance than S. fluorescense or C. marvescence when exposed to essential oils of rosemary, garlic and thyme (Farag et al., 1989). Mutated E. coli and S. aureus are resistant against essential oils of pine (Moken et al., 1997).

In recent years, scientific results have shown that pharmaceutically extracted compounds belong to phenolic compounds, vitamins and tannins with striking antioxidant activity (Suffredini et al., 2004). Many papers have been published on the basis of the possible antimicrobial activities of medicinal herbs against gram positive and gram negative bacteria (Evans et al., 2002). Both negative and positive gram bacteria could be responsible for various ailments. For instance, gram (+) bacteria like Staphylococcus aureus could create wound infection, toxic shock syndrome and food poisoning (Benayache et al., 2001) while gram (-) bacteria like E. coli is the main reason of diarrheea in human, and also can cause coleoyctesic or septicaemia (Benhassaini et al., 2003). Among recently detected infections, those caused by Methicillin-resistant Staphylococcus aureus (MRSA) are of great importance owing to their high adaptability in overcoming almost all antibiotics (Lambert and Pearson, 2000). Clinical antibiograms available in the market (Adwan et al., 2009). As previously stated, a problematic issue in destroying the pathogens might be their adaptability to antibiotics and application of herbal medicine might be a superior candidate to control them.

Pathogens employ various mechanisms to control antibiotics like specialized efflux systems. One of the other pathogen that is resistant to different available antibiotics, P. aeroginosa enjoys the mentioned strategy to overcome antibiotics (Elbashiti et al., 2011). Another mechanism to protect pathogens against antibiotics is the production of extended-spectrum β lactamases (ESBLs) enzymes (Durwish and Abarjui, 2010).

CONCLUSION

Generated flavors through application of essential oils, presence of the aromatic components in medicinal herbs together with necessities to high-cost methods in order to find antimicrobial agents among bioactive components have limited the use of essential oils as antimicrobial agents. Application of such compounds should be under an accurate selection system along with evaluation of their antimicrobial potentials in the least concentrations. Incorporation of essential oils to food formulate or using them, either alone, in combination with other chemical preservatives, could favor their synergistic effects in fighting against various infections and spoilage. The prospect of synergistic effect of the simultaneous application of various spices and medicinal herbs in designing new drugs and replacing chemical drugs with such sources would be of great importance in future research studies.
## Table 1 Some recently published studies on the application of herbal drugs in fighting against pathogens

<table>
<thead>
<tr>
<th>Name</th>
<th>Used section</th>
<th>Used solvent or extraction technique</th>
<th>Targeted Microorganism</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bailota bullata</em> Pomel</td>
<td>aerial parts</td>
<td>Ethyl acetate, chloroform</td>
<td><em>E. coli, P. aeruginosa, Klebsiella sp, S. pneumoniae</em></td>
<td>Adeeyo et al., 2020</td>
</tr>
<tr>
<td><em>Centaurea hypoleuca</em> L.</td>
<td>Roots</td>
<td>methanol, chloroform, hexane and aqueous</td>
<td><em>B. subtilis, B. cereus, S. aureus, Typhimurium, A. fumigatus, C. albicans</em></td>
<td>El mokni et al., 2020</td>
</tr>
<tr>
<td><em>Eleaegnus indica</em></td>
<td>Aerial parts</td>
<td>Ethanol extract</td>
<td><em>S. aureus, E. coli, P. aeruginosa, C. albicans and E. coli, ATCC 6539</em></td>
<td>Al-elaham et al., 2020</td>
</tr>
<tr>
<td><em>Leptadenia hastata</em></td>
<td>leaves</td>
<td>methanol</td>
<td><em>C. albicans, A. fumigatus, C. neoformans, E. coli, P. aeruginosa, K. pneumoniae, V. resistance enterococcus, MRSA</em></td>
<td>Beloo et al., 2018</td>
</tr>
<tr>
<td><em>Zanzoxylum zanthoxyloides</em> and G. latifolium*</td>
<td>aerial parts, ethyl acetate, chloroform</td>
<td></td>
<td><em>E. coli, P. aeruginosa, Klebsiella sp, S. pneumoniae</em></td>
<td>Adeeyo et al., 2020</td>
</tr>
<tr>
<td><em>Nauclea latifolia</em> Smith.</td>
<td>Whole fruit</td>
<td>n-hexane, ethylacetate, n-butanol</td>
<td><em>S. aureus, S. sonnei</em></td>
<td>Oyedeci-Amusa and Ashafa, 2019</td>
</tr>
<tr>
<td><em>F. dettoidea</em></td>
<td>leaves</td>
<td>Chloroform, methanol methanol chloroform,</td>
<td><em>S. aureus</em></td>
<td>Ashraf et al., 2019</td>
</tr>
<tr>
<td><em>Orthosiphon stamineus</em></td>
<td>leaves</td>
<td>methanolic, aqueous, ethyl acetate</td>
<td><em>P. mirabilis, K. pneumonia</em></td>
<td>Blonk and Cock, 2019</td>
</tr>
<tr>
<td><em>Piptoporum angustifolium</em></td>
<td>Aerial parts</td>
<td>Hydro distillation</td>
<td><em>C. albicans</em></td>
<td>Tian et al., 2019</td>
</tr>
<tr>
<td><em>Pungens</em></td>
<td>flower, leaf, stem and root</td>
<td>methanol</td>
<td><em>MRSA</em></td>
<td>Abdi and Dego, 2019</td>
</tr>
<tr>
<td><em>Eleaegnus indica</em></td>
<td>Aerial parts</td>
<td>Acetone, hexane</td>
<td><em>M. racemous</em></td>
<td>Srinivasana et al., 2019</td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>Aerial parts</td>
<td>Ethyl acetate</td>
<td><em>E. coli, E. faecalis</em></td>
<td>Srinivasana et al., 2019</td>
</tr>
<tr>
<td><em>Amaranthus spinosus</em></td>
<td>aerial parts</td>
<td>Methanol</td>
<td><em>S. epidermidis, S. typhi, S. Typhimurium</em></td>
<td>Srinivasana et al., 2019</td>
</tr>
<tr>
<td><em>L. angustifolia, C. citratus and M. piperita</em></td>
<td>leaves</td>
<td>Ethanol extract</td>
<td><em>S. aureus, E. coli and C. albicans</em></td>
<td>Gishen et al., 2020</td>
</tr>
<tr>
<td><em>Citrus sinensis</em></td>
<td>seed oil</td>
<td>n-hexane, methanol</td>
<td><em>S. marcescens, E. coli, S. Typhimurium, P. aeruginosa, C. albicans</em></td>
<td>Atolani et al., 2020</td>
</tr>
<tr>
<td><em>P. amarus</em></td>
<td>leaves</td>
<td>ethanolic extract</td>
<td><em>S. marcescens, E. coli, S. Typhimurium, P. aeruginosa, C. albicans</em></td>
<td>Maria Braga Ribeiroa et al., 2019</td>
</tr>
<tr>
<td><em>Aerva lanata</em></td>
<td>whole plant</td>
<td>Chloroform, Ethyl acetate Water methanol</td>
<td><em>E. coli, E. aerogenes</em></td>
<td>Al-ansari et al., 2019</td>
</tr>
<tr>
<td><em>Rubus fruticosus Lried</em></td>
<td>leaves</td>
<td>Methanol, hexane, ethyl acetate, Hydro alcoholic, Chloroform</td>
<td><em>E. faecalis, S. aureus, E. coli, H. influenza</em></td>
<td>Welia et al., 2020</td>
</tr>
<tr>
<td><em>Achillea cucullata</em></td>
<td>aerial parts</td>
<td>Ethanolic extraction</td>
<td><em>S. aureus, E. faecalis, P. aeruginosa, E. coli, C. albicans</em></td>
<td>Eruygur et al., 2018</td>
</tr>
<tr>
<td><em>Lepidium sativum</em></td>
<td>seed oil</td>
<td>Ethanolic extract</td>
<td><em>S. aureus, B. subtilis, E. coli, P. aeruginosa, S. enterica, K. pneumoniae, C. albicans</em></td>
<td>Alqahtani et al., 2018</td>
</tr>
<tr>
<td><em>Centaura hypoleuca</em></td>
<td>stem</td>
<td>Ethyl acetate</td>
<td><em>S. aureus, B. subtilis, E. coli, P. aeruginosa, S. enterica, K. pneumoniae, C. albicans</em></td>
<td>Ozcan et al., 2019</td>
</tr>
<tr>
<td><em>C. hypoleuca</em></td>
<td>Ethyl acetate, methanol flower, Methanol Ethyl acetate flower, stem</td>
<td></td>
<td><em>C. albicans</em></td>
<td>Ozcan et al., 2019</td>
</tr>
<tr>
<td><em>C. hypoleuca</em></td>
<td>Ethyl acetate, methanol flower, Methanol Ethyl acetate flower, stem</td>
<td></td>
<td><em>C. albicans</em></td>
<td>Ozcan et al., 2019</td>
</tr>
</tbody>
</table>
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