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Topical Oral Medicaments in Traditional Persian Medicine

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Abstract

Objectives: Traditional, topically used oral medicaments are of great importance in the treatment of both oral and systemic diseases. Therefore, the aim of this study was to review the indications of various drug delivery forms and active ingredients of currently used medications in complementary medicine, as well as the results of recent research to find any possible conformity between their traditional and recent pharmaceutical properties.

Methods: In this review article, different resources including electronica databases, hand searching, the screening of reference lists and contacting experts were extensively performed, followed by categorizing the extracted data.

Results: Based on the results, 6 drug forms were found in gaseous, liquid, and solid states with more than 70 formulations. Liquid and gaseous forms were mainly used to manage systemic conditions and solid forms were mainly applied for local treatments. In addition, the investigation of about 50 herbal components showed that the traditional therapeutic effects of the vast majority of the ingredients were in line with those of the recent studies. However, no clinical studies were found regarding the traditionally mentioned systemic effects after the topical use of this medicament in the form of gargles or mouthrinse.

Conclusions: In general, the side effects of oral and injectable drugs, as well as the specific advantages of oral mucosa in achieving the topical and systemic effects and the variety of the plant components of Iranian traditional oral medicament might have high potentials for finding new drugs and improving treatment strategies of some systemic diseases such as central nervous system diseases and depression.

Keywords: Ethno-medicine, Ethno-pharmacology, Traditional Persian medicine, Oral, medicaments

Introduction

The history of the topical use of medications in the mouth goes back to 5000-3000 BC. Ancient Egyptians used a combination of powdered ashes from oxen hooves, Myrrha, eggshell, and pumice to remove the mass from the tooth. About 1000 BC, ancient Iranians added materials such as the burnt shells of the snails, herbs, gypsums, and oysters to these formulations (1). On the other hand, oral health is significantly important for retaining the general health and quality of life. In addition, maintaining oral hygiene, along with having healthy and beautiful teeth leads to positive psychological effects, which could enhance the self-confidence of the individuals (2). Previous research has focused on the link between oral-dental infections and systemic diseases such as cardiovascular diseases and diabetes (3). Further, oral and dental diseases impose a high cost on global economy systems both as direct and indirect treatment costs (4). Therefore, improving the level of oral health and preventative measures can help maintain the financial resources of the countries by reducing the costs while increasing efficiency. On the other hand, several side effects of oral and parenteral drugs and the great advantages of trans-mucosal drug delivery systems including high vascular bed and permeability, the avoidance of first-pass and enzymatic degradation, and the pre-systematic elimination have increased the tendency to use these drug delivery routes in recent years (5).

Among the transmucosal routes, the buccal route has notable importance in designing new drugs due to the ease of use, high acceptability, along with the possibility of easily observing localized complications and having a high level of recovery rate in oral tissues (5). In traditional Persian medicine (TPM) texts, various drug delivery forms are introduced for topical use in the mouth. Notably, the mentioned medicaments are generally comprised of diverse medicinal plants (6). Approximately 50 herbal remedies belonging to 40 plant families are used in the formulation of these drugs. Furthermore, they have antimicrobial (75%), anti-inflammatory (55%), and anti-oxidant (40%) properties. In addition, recent research has confirmed anti-epilepsy, antipyretic, sedative, anti-asthmatic, bronchodilator, and anti-parkinsonism properties for these herbal components (See Supplementary data, Table S1). Moreover, these drug forms are utilized to achieve systemic and topical treatment goals. To the best of our knowledge, no centralized and focused studies are

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available regarding the topical oral medicaments in the TPM. Considering the above-mentioned discussions, the present study attempted to investigate the topical oral dosage forms in the TPM and the extraction of their medicinal plants. Finally, the results of recent studies on the pharmacological properties of plant components were compared with their traditional uses in order to find any conformity.

Evidence Acquisition

In this study, the most repeated traditional topical oral dosage forms, along with their components were extracted from the TPM pharmaceutical manuscripts defined as *Gharabadines*. *Gharabadines* or ancient pharmacopeias discuss diverse types of the ancient dosage forms, ingredients, procedures of preparation, dosage, indications, maintenance conditions, as well as the best time of their usage and other related issues. Among them, Canon-e-Medicine (7), Gharabadine-e-Ghaderi (8), and Gharabadin-e-Salehi, (9) are more notable. *Makhzan-ol-Advieh* (10), which is of colossal significance among the TPM manuscripts, was used as well. The examples of the most repetitive formulations of topically used oral dosage forms and their therapeutic uses are provided in Table S2 (see Supplementary data). Moreover, Table S1 presents the results of recent studies on the pharmacological properties of the medicinal plants used in these formulations, along with their topical and systemic effects. Additionally, the scientific names of medicinal plants are authenticated using the botanical textbook of Popular Medicinal Plants of Iran (11). Databases such as Science Direct, PubMed, Scopus, and finally, Google Scholar were thoroughly investigated in this regard.

In reviewing TPM literature, 6 forms of oral topical dosage forms were extracted as follows:

1. Bakhoorate (oral fumigations): They are specific to the problems of the oral cavity and systemic diseases. Hence, the medicament is burnt and the organ is exposed to the resultant smoke to make this dosage form. Notably, the smoke is delivered to the mouth either directly using a narrow tube or by using special devices (9). Their therapeutic goals include local problems including toothache and systemic diseases such as asthma, cough, and cardiac disorders (6).

2. Gharagher (gargles): They are considered as liquid dosage forms, which patients exert and turn in the mouth for a while and then evacuate. This action is repeated several times. To prepare gargles, medicaments are dissolved in liquids such as water, vinegar, rose water, oxymel syrup, or in other plant extracts (6). The ancient indications of characters are mostly for systemic diseases such as nasal congestion and runny nose, coughing, eye problems, facial paralysis, as well as some oral problems such as oral and tongue wounds, aphtha, and tonsillitis (6).

3. Mazmazeh: As liquid dosage forms, they are similar to gargles. The difference is that mazmazehes are mostly used for oral problems such as aphtha, toothache whereas gargles are mainly used for systemic diseases (7).

4. Sanoonate (oral doughes): All ingredients are thinly powdered in this dosage form. They are soaked with saliva or herbal extracts and rubbed on the teeth and gums when using (8). It should be kept on the teeth for at least two hours as well (9). This dosage form is extensively used for oral and dental diseases (6). The particle size of each component varies based on the application. However, those used for gum disorders should have finer particle sizes compared to those used for teeth whitening (6). In addition, they are mostly used in cases such as gingival and palatal ulcers, teeth whitening, and the elimination of bad breath odor in addition to the discontinuation of gingival bleedings, toothache, and teeth loosening (9).

5. Zarorate (oral powders): These powdered solid drugs are spread on the teeth and gums. Unlike sanoonate, these are used in the form of dry powder and there is no need to become macerated with herbal extracts. Further, the therapeutic indications are similar to those of sanoonate (9).

6. Baroodate: The word of barood literally means cooler. The purpose of using these medicaments is to create a sense of cooling in the oral mucosa. In the process of making these drugs, the solid materials are changed to very soft powders, which are mixed with mostly cold temperament fluids and then dried (6).

Ancient Persian physicians used different materials, mainly plants, to make these products. Table S2 summarizes various parts of medicinal plants such as the seeds, roots, leaves, branches, flowers, and gums which were utilized in order to prepare the mentioned dosage forms. Moreover, minerals such as salt, white coral, shell, clay, as well as organic materials derived from animals were used to prepare oral topical dosage forms. Traditional physicians used to mix the powdered drug components with appropriate fluids and dry them up in the form of pills for the ease of transportation of liquid dosage forms, and finally, they solved them again in the suitable solvents at the time of use.

Discussion

This study was conducted with the aim of extracting various local oral herbal remedies used by ancient physicians during 9-18 centuries AD. First, the study tried to investigate the components and indications of their formulations and the results of recent studies in this regard to present new perspectives. To this end, 6 drug forms in three solid, liquid, and gaseous states were used by medieval Iranian physicians during 9-18 centuries AD (6). Since then the variety of these drug forms has not extremely changed, but their indications are highly limited. Their main materials included medicinal plants, followed by minerals and animal derivatives (9). Almost 50 different herbs belonging to nearly 40 families were used in this section and all parts of the plants including

the seed, fruit, aerial parts, oleo gum resin, and rhizome were utilized in their formulations (Table 2). Of the 6 drug forms mentioned in the ITM sources, bakhorate (oral fumigations), which is similar to those of recent sprays, is mainly used in systemic diseases and for oral problems in some cases (6). For instance, the smoke resulting from burning *Peganum harmala*' seeds is recommended for a toothache (8). Faridi et al found that the amount of alfa-pinene as the main part of antimicrobial properties in the essential oil and smoke of *Peganum harmala* seeds was 76.2% and 60.4%, respectively. In addition, there was a certain amount of styrene and other compounds with potentially antimicrobial and immunomodulatory effects in the smoke which were not present in the volatile oil (12). The results of another study showed that the active alkaloids of the *Peganum harmala* seeds had analgesic effects that are applied both centrally and peripherally (13) . In another formulation, smoke resulting from burning the aerial parts of *Anethum graveolens* was used for a toothache (6). In a traditional formulation, the resultant smoke of *A. graveolens* was recommended for relieving the inflammation of the oral cavity (8). According to our knowledge, no study has addressed the chemical properties of *A. graveolens* smoke although the extract and essential oil of *A. graveolens* seeds demonstrated anti-inflammatory, antimicrobial, and analgesic properties (14,15). Hence, oral topical liquid products are now used predominantly for oral and dental problems while they have more extensive indications in the TPM. The gargles and maximizes, as two liquid pharmaceutical forms, were obtained from boiling or dissolving medicinal plants in solvents such as water, oxymel syrup, and vinegar. Traditional medicine scholars believed that the collapse of the ecological balance in each part of the body causes the disease and the therapeutic effect of gargles is due to the secretion of intrusive material in the oral cavity and the return balance to that part (7). Due to the bitter taste of most plant extracts, sweeteners such as honey and oxymel syrup are used to improve their taste. The use of honey as a sweetener is also effective in improving the flavor of these products. Further, the presence of phenolic compounds in honey manifests the antimicrobial property of these products. The result of a comparative study regarding the anti-plaque effects of honey and chlorhexidine mouthwash revealed that honey mouthwash was more effective than chlorhexidine mouthwash in reducing dental plaques (16). Furthermore, the use of oxymel syrup (containing honey and vinegar with a specific ratio) probably with different potential mechanisms such as increasing the permeability and astringency of the gingival tissue improves the therapeutic effects of mouth rinse (10). In some cases, oral topical liquids should be used warm or half warm (7) since heat causes vasodilatation and increases the permeability of the vessels and local absorption of medicines.

Solid products are dry powders and are wetted with saliva and rubbed on the teeth in the time of use. The abrasives are the most important part of modern toothpaste. The most commonly used abrasives include SiO_2, $CaHPO_4$, and $CaCO_3$. The particle size of the abrasives is highly important in achieving the proper quality of the toothpaste. Moreover, the coarsening of the abrasive particles causes the scratching of the enamel and feeling unwell. Medieval Persians used mineral materials such as clay and animal derivatives such as snail shells and horseradish horns in solid dosage forms. Additionally, they used a special process called "EHRAGH" in order to facilitate the crushing of these materials (10). This process was considered as one of the stages in preparing the materials, especially in manufacturing ophthalmic products (9). This action not only facilitates their powdering but also reduces the microbial load of the product. Badeeb et al (17) reported no microbial contamination in their study on the microbial content of an Iranian traditional ophthalmic product (Kohl, which is prepared by the above-mentioned method).

Although traditional tooth doughs were used in oral and dental problems, their indications were more diverse compared to the modern ones. In addition to the usual indications, they also were used for other purposes such as discontinuing gingival bleeding, loosening of the teeth, or hardening of the gum (9). The investigation of traditional topical oral medicaments showed that a majority of them, especially in liquid dosage forms were used for systemic diseases which mainly included the central nervous system (CNS), along with respiratory and cardiovascular diseases (8). Table S2 demonstrated the result of recent research on about 50 different medicinal plants based on their local and systemic effects. In this classification, antimicrobial, anti-inflammatory, antioxidant, and wound healing properties were considered as topical effects and the effects on the CNC, and respiratory and cardiovascular systems were classified as systemic effects. Due to the attributed systemic effects in the TPM manuscripts, the pharmacological properties of the studied plants, including the diseases of the CNS, along with respiratory, and cardiovascular systems were represented as their systemic effects (Table S2). Nearly 98% and 57% of the plants in the study showed topical and systemic effects (Figure 1). The CNS effects (i.e., hypnotic, sedative, antidepressant, antipyretic, Ache and Bche inhibitory, memory enhancing, anti-epileptic, monoamine oxidase inhibitory, and neuroprotective effects) were the most common systemic effects (Figure 1). The remedies of the respiratory system disease entitled "anti-asthmatic, bronchodilator, and expectorant effects, along with cardiovascular effects including increasing the heart rate and cardiac stimulant activity" were observed in the next stage (Figure 2). The comparison of Tables S1 and S2 revealed that there is conformity between the traditional treatment goals and the recent research results in many cases. For example, plants such as *Anacyclus pyrethrum, Zataria multiflora, Nigella sativa*, and *Zingiber officials* were used in the formulation of a gargle

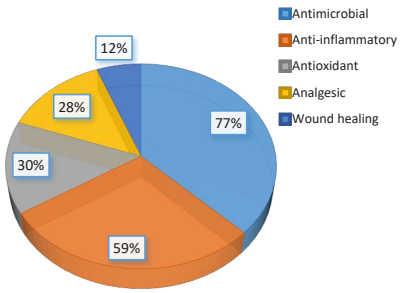

Figure 1. Local Effects of Medicinal Plants Used in TPM Topical Oral Dosage Forms

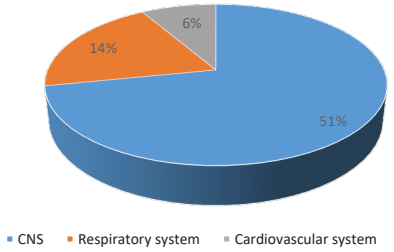

Figure 2. Systemic Effects of Medicinal Plants Used in TPM Topical Oral Dosage Forms.

recommended to treat a headache, the complications of a stroke, the tremor and paralysis of face muscles (Table S1). The examination of their pharmacological properties indicated that all these plants in the formulation had some kind of characteristics associated with their traditional indications. The anti-nociceptive, anti-inflammatory, ant epileptogenic, and neuroprotective properties for *Nigella sativa* (18), as well as anti-nociceptive, anxiolytic, memory-enhancing properties for *Anacyclus pyrethrum* (19). The other properties such as sedative and CNS depressant for *Acorus calamus* (20, 21) and anti-hypertensive activity in *Apium graveolens* (22-24) revealed that each of them plays a role in the overall healing effects. As described above, the research result is compatible with their traditional therapeutic goals in the case of *Peganum harmala* and *Anethum graveolens* smoke.

Limitations

It goes without saying that many traditional therapeutic effects are not approved yet. Accordingly, sufficient laboratory and clinical research is required to confirm or reject the therapeutic effects of the previously mentioned herbs. For instance, conducting adequate research could be a good idea for clinical treatments, especially in the field of systemic therapeutic effects of gargles and mouthwashes on the CNS.

Although in recent years many ideas of traditional medicine schools have been used in herbal remedies and treatment of diseases, it seems that there are many neglected contents. A remarkable point about topical oral traditional products, in addition to the variety of their ingredients, is their systemic use in the CNS, as well as respiratory and cardiovascular diseases. Considering the high percentage of people involved in these diseases and the variety and multiplicity of oral consumed drugs, the possibility of the side effects of the digestive tract is unavoidable. Therefore, the use of oral topical products with systemic effects can be a good option. This article, which contains information on the components and their traditional uses, maybe helpful in this field and provides new perspectives in the treatment of diseases such as Alzheimer, depression, Parkinson, epilepsy, hypertension, and the like.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran (code number: 1396.161.REC).

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Supplementary Data

Supplementary file 1 contains Tables S1-S2.

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