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Pharmacodynamic Evaluation of Polyherbs and its Formulation for Antitussive Activity Using Citric Acid Induced in Guinea Pig

Research Article

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Abstract

This review article focuses on the pharmacodynamic evaluation of polyherbal formulations for antitussive activity, utilising a citric acid-induced cough model in guinea pigs. The study explores various polyherbs traditionally used in cough treatment, aiming to validate their efficacy through scientific methods. By inducing coughing in guinea pigs with citric acid, the antitussive effects of different herbal combinations are assessed in comparison to standard cough suppressants. The review emphasizes the potential advantages of polyherbs, such as synergistic effects, reduced side effects, and natural origin, making them promising candidates for cough management. Furthermore, the article highlights the importance of evaluating dosage, formulation, and bioactive components to optimize therapeutic outcomes. This comprehensive review contributes to the growing body of evidence supporting the use of polyherbal remedies in the treatment of cough-related disorders.

Keywords: Polyherbal formulation, Antitussive activity, Citric acid-induced cough, Guinea pig model, Pharmacodynamics.

Introduction

Polyherbal formulations are combinations of two or more medicinal herbs designed to enhance therapeutic efficacy and reduce adverse effects. These formulations have been a fundamental part of traditional medicine systems, such as Ayurveda, Traditional Chinese Medicine (TCM), and Unani, for thousands of years. In these systems, multiple herbs are often combined to treat complex health conditions, utilising the synergistic effects of various plant compounds to target multiple biological pathways simultaneously (1).

This holistic approach is particularly beneficial in managing respiratory conditions like coughs and bronchitis, where different herbs can work together to relieve symptoms and address underlying causes.

The study of pharmacodynamics is crucial for understanding how polyherbal formulations work, especially for their antitussive (cough-suppressing) activity. By investigating the pharmacodynamic properties, researchers can determine how these formulations influence physiological processes, their mechanisms of action, and how they interact with the body to suppress cough.

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Overview of polyherbal formulations in traditional medicine

Polyherbal formulations have been an integral part of traditional medicine systems like Ayurveda, Traditional Chinese Medicine (TCM), Unani, and many indigenous healing practices worldwide. These formulations involve combining two or more herbs to achieve a desired therapeutic effect, based on the principle that the synergistic interaction between different plant compounds can enhance efficacy and reduce toxicity compared to single-herb remedies (2).

In traditional medicine, polyherbal formulations are meticulously crafted, often following ancient texts or local knowledge passed down through generations. The combinations are designed to address complex health conditions holistically, targeting multiple biological pathways simultaneously. For instance, a formulation aimed at respiratory health may include herbs that not only suppress cough but also reduce inflammation, fight infection, and strengthen the immune system (3).

Importance of studying their pharmacodynamics for antitussive activity

Studying the pharmacodynamics of polyherbal formulations for antitussive activity is vital to understanding how these complex mixtures work to alleviate cough. Pharmacodynamics involves analyzing how the active compounds within these herbs interact with the body to produce therapeutic effects. For antitussive activity, it's important to know which components are responsible for suppressing the cough reflex and how they modulate various physiological pathways, such as those involving the central nervous system, immune response, and inflammatory processes.

Understanding the pharmacodynamics allows researchers to optimize the herbal combinations and dosages to maximize efficacy and minimize side effects. Since polyherbal formulations are often composed of multiple active compounds, studying their interactions is crucial to ensuring that they work synergistically rather than antagonistically. This knowledge helps in refining traditional herbal practices and provides a scientific basis for their use in modern medicine (4).

Moreover, such studies can lead to the discovery of novel bioactive compounds with potent antitussive properties, potentially contributing to the development of new medications. By validating the effectiveness of these herbal formulations through pharmacodynamic research, healthcare providers can have greater confidence in prescribing these treatments, ultimately benefiting patients with safer and more effective options for managing cough and related respiratory conditions (5).

Rationale for herb selection

Criteria for Selecting Specific Herbs in the Formulation

The selection of specific herbs for a polyherbal formulation is guided by several key criteria. Firstly, the herbs are chosen based on their known pharmacological activities that align with the therapeutic goals of the formulation, such as antitussive, anti-inflammatory, or antimicrobial effects. Secondly, the safety profile of each herb is crucial, ensuring minimal side effects and toxicity when used individually and in combination. Thirdly, the potential for synergistic effects is considered, where the combined use of herbs enhances efficacy more than any single herb alone. Additionally, traditional use and historical efficacy in treating similar conditions play a significant role in herb selection, providing a foundation of empirical knowledge that supports their inclusion in the formulation. Finally, availability and sustainability of the herbs are considered to ensure that the formulation is accessible and environmentally responsible (6).

Ethnopharmacological Background of Each Herb Used:(7)

1. ***Curcuma zedoaria* (Dried Rhizomes):** Traditionally used in Ayurvedic and traditional Chinese medicine for its anti-inflammatory, antimicrobial, and digestive properties. It is believed to support respiratory health by reducing mucus production and inflammation.
2. ***Salvadora persica* (Dried Leaves):** Commonly known as the toothbrush tree or miswak, its leaves have been used in various cultures for oral hygiene and respiratory ailments, attributed to their antimicrobial and anti-inflammatory properties.
3. ***Glycyrrhiza glabra* (Dried Roots):** Widely used in traditional medicine for its demulcent, expectorant, and anti-inflammatory effects, particularly beneficial for soothing irritated mucous membranes in the respiratory tract.
4. ***Andrographis paniculata* (Dried Leaves):** Known for its bitter taste and potent immunomodulatory, anti-inflammatory, and antiviral properties, this herb is used extensively in Ayurvedic and traditional Chinese medicine to treat respiratory infections and boost immune responses.
5. ***Ocimum tenuiflorum* (Dried Leaves):** Also known as Holy Basil or Tulsi, it is revered in Ayurveda for its adaptogenic, antimicrobial, and anti-inflammatory properties, making it a common remedy for respiratory conditions and overall health enhancement.

Pharmacological profile of each herb

***Curcuma zedoaria* Rosc. (Dried Rhizomes)**

Curcuma zedoaria, also known as white turmeric, has been traditionally used in Ayurvedic and traditional Chinese medicine to treat a variety of ailments, including respiratory disorders, digestive issues, and inflammatory conditions (8). The rhizomes of *Curcuma zedoaria* are known for their anti-inflammatory, antimicrobial, and antioxidant properties (9). These pharmacological actions are attributed to the presence of curcuminoids and essential oils, which help reduce inflammation, inhibit microbial growth, and neutralize free radicals (10).

***Salvadora persica* (Dried Leaves)**

Salvadora persica, commonly known as the toothbrush tree or miswak, has a long history of use in traditional medicine for oral hygiene and respiratory health (11, 12). The dried leaves of *Salvadora persica* contain a variety of active compounds, including alkaloids, flavonoids, and saponins, which possess antibacterial, anti-inflammatory, and antioxidant properties (13). These compounds help protect the respiratory tract from infections, reduce inflammation, and support overall respiratory health (14).

***Glycyrrhiza glabra* (Dried Roots)**

Glycyrrhiza glabra, commonly known as licorice root, contains several bioactive constituents, including glycyrrhizin, flavonoids, and saponins (15). Glycyrrhizin, the primary active compound, is known for its anti-inflammatory, expectorant, and demulcent properties, making it effective in soothing irritated mucous membranes and reducing cough reflexes. Flavonoids and saponins further enhance its expectorant effects, helping to clear mucus from the airways, thereby providing relief from cough and respiratory discomfort (16).

***Andrographis paniculata* (Dried Leaves)**

Andrographis paniculata, often referred to as the "King of Bitters," is renowned for its potent immunomodulatory, anti-inflammatory, and antiviral properties. The dried leaves contain active compounds like andrographolides, which inhibit pro-inflammatory cytokines and enhance immune responses, making the herb effective in managing respiratory infections and reducing cough. Andrographolides also exhibit bronchodilatory effects, helping to open up airways and improve breathing, which contributes to its antitussive activity (17).

Ocimum tenuiflorum (Dried Leaves)

Ocimum tenuiflorum, commonly known as Holy Basil or Tulsi, is highly regarded in Ayurveda for its adaptogenic, antimicrobial, and anti-inflammatory properties. Several studies have demonstrated its effectiveness in treating respiratory disorders, including asthma, bronchitis, and coughs(18). The dried leaves of Tulsi contain essential oils, such as eugenol and camphor, which help reduce inflammation, enhance immune function, and clear respiratory passages. Additionally, its antioxidant properties protect the respiratory tract from damage caused by oxidative stress, further supporting its use in respiratory health (19).

Pharmacognostical profile of each herb

Curcuma zedoaria Rosc. (Dried Rhizomes) (20, 21, 22).

- **Biological Source:** Curcuma zedoaria, commonly known as "Zedoary," is derived from the dried rhizomes of *Curcuma zedoaria* (figure 1).
- **Family:** Zingiberaceae

Figure 1: Dried Rhizomes of _Curcuma zedoaria_ (23)

- **Morphological Characteristics**: The rhizomes are large, cylindrical, and branched, with a diameter ranging from 2-4 cm. They are covered in a light brown skin, which becomes darker when dried. The inner part of the rhizome is yellowish-brown, with a distinctive aromatic odour. The taste is slightly bitter and pungent.
- **Microscopy**: The microscopic examination reveals parenchymatous cells filled with starch grains, fibrovascular bundles, and scattered oil cells. The rhizomes show well-defined cork layers, prominent vascular bundles, and the presence of yellowish-brown oil globules.
- **Phytochemical Constituents**: Major constituents include curcuminoids (curcumin, demethoxy curcumin), essential oils (zingiberene, curzerenone), and sesquiterpenoids.
- **Pharmacological Properties**: Known for anti-inflammatory, antioxidant, and antimicrobial activities. Traditionally used for digestive and respiratory ailments.

Salvadora persica (Dried Leaves) (24, 25)

- **Biological Source**: Derived from the dried leaves of *Salvadora persica* (figure 2), commonly known as the "Toothbrush Tree" or "Miswak."
- **Family**: Salvadoraceae
- **Morphological Characteristics**: The leaves are simple, alternate, and small, measuring about 4-6 cm in length. They are greenish when fresh and turn greenish-brown when dried. The shape is elliptical or lanceolate with entire margins, and the surface is smooth with a slightly bitter taste.

Figure 2: Leaves _Salvadora persica_ (26).

- **Microscopy**: Microscopic examination reveals an epidermis covered with a cuticle, parenchymatous cells containing calcium oxalate crystals, and scattered oil cells. The vascular bundles are small, with a few fibers surrounding them.
- **Phytochemical Constituents**: The primary constituents are alkaloids (salvadorine), flavonoids, tannins, saponins, and essential oils (including sulfur-containing compounds).
- **Pharmacological Properties**: Exhibits antimicrobial, anti-inflammatory, and analgesic properties. Traditionally used in oral hygiene and respiratory health.

Glycyrrhiza glabra (Dried Roots) (27, 28).

- **Biological Source**: The dried roots of Glycyrrhizaglabra (figure 3), commonly known as “Licorice.”
- **Family**: Fabaceae

Figure 3: Dried Roots Glycyrrhizaglabra (29)

- **Morphological Characteristics**: The roots are cylindrical, slightly twisted, and measure about 1-2 cm in diameter. The outer surface is yellowish-brown, and the inner part is pale yellow. The taste is sweet due to the high content of glycyrrhizin, a compound that is 50 times sweeter than sugar.
- **Microscopy**: The root shows medullary rays, parenchyma with starch grains, and prominent laticifers (latex cells). The vascular bundles are arranged radially, and the presence of tracheids and fibers is common.
- **Phytochemical Constituents**: The roots contain glycyrrhizin, glycyrrhizic acid, flavonoids (liquiritin), saponins, and coumarins.
- **Pharmacological Properties**:Possesses expectorant, anti-inflammatory, and antitussive properties. Widely used for cough suppression.

***Andrographis paniculata* (Dried Leaves)[30].**

- **Biological Source**: The dried leaves of *Andrographis paniculata* (figure 4), commonly known as "*Kalmegh*."
- **Family**: Acanthaceae

Figure 4: Dried Leaves of *Andrographis paniculata* (31)

- **Morphological Characteristics**: The leaves are simple, opposite, and lanceolate, with a dark green color when fresh and pale green when dried. They have a characteristic bitter taste.
- **Microscopy**: Microscopic analysis shows the presence of glandular and non-glandular trichomes, abundant stomata, and elongated vascular bundles. The epidermis is covered with a thick cuticle.
- **Phytochemical Constituents**: The major constituents include andrographolides (a diterpenoid lactone), flavonoids, and diterpenes.
- **Pharmacological Properties**:Known for its anti-inflammatory, antiviral, and immune-boosting effects. Used in respiratory infections and fever management.

***Ocimum tenuiflorum* (Dried Leaves) (32, 33)**

- **Biological Source**: Derived from the dried leaves of *Ocimum tenuiflorum* (figure 5), commonly known as "Holy Basil" or "*Tulsi*."
- **Family**: Lamiaceae

Figure 5: Derived leaves of *Ocimum tenuiflorum* (34)

- **Morphological Characteristics**: The leaves are small, ovate, and slightly toothed. They are greenish when fresh and dark brown when dried. The surface of the leaves is covered with fine hairs, and they have a strong, aromatic scent.
- **Microscopy**: The leaf microscopy shows glandular trichomes, stomata, and well-developed vascular bundles. The epidermal cells contain calcium oxalate crystals, and the mesophyll consists of loosely arranged cells.
- **Phytochemical Constituents**: The main constituents include essential oils (eugenol, ursolic acid), flavonoids, and tannins.
- **Pharmacological Properties**:Demonstrates anti-inflammatory, antitussive, and expectorant properties. Traditionally used for respiratory and cold-related ailments.

Phytochemical screening of each herb for antitussive activity

Phytochemical screening is crucial for identifying the bioactive compounds present in medicinal plants. The following is a review of the major phytochemicals found in *Curcuma zedoaria*, *Salvadorapersica*, *Glycyrrhizaglabra*, *Andrographispaniculata*, and *Ocimumtenuiflorum*, and their potential roles in antitussive activity.

Curcuma zedoaria (Dried Rhizomes) (35)

Phytochemical Constituents

- **Curcuminoids**: These are the primary active constituents, including curcumin, demethoxycurcumin, and bisdemethoxycurcumin. These compounds are known for their anti-inflammatory, antioxidant, and antimicrobial properties.
- **Essential Oils**: These include camphor, curzerenone, and zedoarol, which have antitussive and anti-inflammatory properties.
- **Terpenes**: These contribute to the plant's anti-inflammatory and bronchodilatory effects.

Role in Antitussive Activity: The anti-inflammatory effects of curcuminoids help reduce airway irritation, while essential oils provide a soothing effect on the respiratory system, which can suppress cough reflexes.

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***Salvadora persica* (Dried Leaves) (36, 37)**

Phytochemical Constituents:

- **Flavonoids**: Compounds such as quercetin and rutin, which exhibit anti-inflammatory and antioxidant properties.
- **Alkaloids**: Salvadorine, which is reported to have analgesic and anti-inflammatory effects.
- **Saponins**: Known for their anti-inflammatory and expectorant properties, aiding in mucus clearance.
- **Tannins**: These astringent compounds have antimicrobial and anti-inflammatory activities.

Role in Antitussive Activity: The anti-inflammatory flavonoids and saponins in *Salvadora persica* help reduce the irritation that triggers coughing. The presence of alkaloids may contribute to its analgesic effects, further aiding in cough suppression.

***Glycyrrhiza glabra* (Dried Roots) (37, 38).**

Phytochemical Constituents

- **Glycyrrhizin**: A triterpenoid saponin that has expectorant, anti-inflammatory, and antiviral properties. It is a key compound for soothing the throat and clearing mucus from the airways.
- **Flavonoids**: Liquiritin, isoliquiritigenin, and glabridin, which possess anti-inflammatory, antioxidant, and antimicrobial properties.
- **Coumarins**: Umbelliferone and herniarin, which have antitussive and bronchodilatory effects.
- **Polysaccharides**: These exhibit immunomodulatory and mucolytic properties, helping to break down mucus.

Role in Antitussive Activity: Glycyrrhizin and flavonoids work synergistically to reduce inflammation and soothe irritated airways. The expectorant properties help clear mucus, which can suppress the cough reflex.

***Andrographis paniculata* (Dried Leaves) (39, 40)**

Phytochemical Constituents

- **Andrographolide**: A diterpene lactone that is the major bioactive compound responsible for anti-inflammatory, antiviral, and immunomodulatory activities. It has also been shown to reduce airway inflammation and irritation.
- **Flavonoids**: Such as andrographin, which have antioxidant and anti-inflammatory effects.
- **Diterpenes**: These contribute to its bronchodilatory effects, helping to reduce airway resistance and cough reflex sensitivity.

Role in Antitussive Activity: The anti-inflammatory effects of andrographolide help suppress cough by reducing inflammation in the respiratory tract. Its antiviral properties also support its use in treating coughs caused by respiratory infections.

***Ocimum tenuiflorum* (Dried Leaves) (41)**

Phytochemical Constituents:

- **Eugenol**: A phenolic compound that exhibits strong antitussive, anti-inflammatory, and antioxidant effects. It helps in soothing the throat and suppressing cough reflexes.
- **Urosolic Acid**: A triterpenoid known for its anti-inflammatory and bronchodilatory properties.
- **Flavonoids**: Apigenin and luteolin, which possess anti-inflammatory and antioxidant activities.
- **Tannins**: Provide antimicrobial and anti-inflammatory effects, supporting the overall health of the respiratory system.

Role in Antitussive Activity: Eugenol is the primary compound responsible for the antitussive activity of *Ocimum tenuiflorum*, helping to suppress the cough reflex. The additional anti-inflammatory and bronchodilatory effects of other compounds, such as ursolic acid, further enhance its efficacy.

Table 1: Summary of Phytochemical Roles in Antitussive Activity (42)

Herb	Phytochemical Constituents	Role in Antitussive Activity
Curcuma zedoaria (Dried Rhizomes)	Curcuminoids, Essential oils (camphor, α-turmerone), Sesquiterpenes	Anti-inflammatory effects reduce airway irritation and inflammation, leading to cough suppression.
Salvadorapersica (Dried Leaves)	Flavonoids, Alkaloids, Saponins, Salvadorine, Tannins	Flavonoids and alkaloids modulate the cough reflex and reduce airway inflammation, alleviating cough symptoms.
Glycyrrhiza glabra (Dried Roots)	Glycyrrhizin, Flavonoids, Saponins, Isoflavones, Coumarins	Glycyrrhizin soothes mucous membranes, reducing cough reflex sensitivity. Flavonoids exert anti-inflammatory and expectorant effects.
Andrographispaniculata (Dried Leaves)	Andrographolide, Flavonoids, Diterpenes, Tannins	Andrographolide provides anti-inflammatory and immunomodulatory effects, reducing airway resistance and coughing.
Ocimumtenuiflorum (Dried Leaves)	Eugenol, Flavonoids, Triterpenoids, Saponins, Alkaloids	Eugenol acts as an antitussive by suppressing cough reflexes and reducing airway inflammation.

Table 1 summarises the key phytochemicals in each herb and their respective roles in reducing cough through mechanisms such as anti-inflammatory action, soothing irritated airways, and modulating the cough reflex. These bioactive compounds work together to provide a synergistic effect in polyherbal formulations for antitussive therapy.

Literature review

In the study of respiratory disorders, the evaluation of polyherbal formulations for their antitussive effects has been a subject of increasing research. The citric acid-induced cough model in guinea pigs is a widely accepted experimental model to assess the effectiveness of such formulations. The following review focuses on the individual herbs used in polyherbal formulations, specifically *Curcuma zedoaria, Salvadora persica, Glycyrrhiza glabra, Andrographis paniculata,* and *Ocimum tenuiflorum*, with reference to their antitussive activity.

***Curcuma zedoaria* (Dried Rhizomes)**

Phytochemical Constituents and Traditional Uses: *Curcuma zedoaria* (Zedoary) is a well-known herb in traditional medicine, valued for its anti-inflammatory, antioxidant, and antimicrobial properties. The active compounds, such as curcuminoids and essential oils, contribute to its pharmacological effects (43).

Antitussive Activity: In a study by Rao et al. (2015), the ethanol extract of *Curcuma zedoaria* was tested on guinea pigs using the citric acid-induced cough model. The results demonstrated a significant reduction in cough frequency compared to the control group, indicating its potential antitussive properties i-inflammatory effect of curcuminoids may contribute to the suppression of cough reflex by reducing airway irritation (44).

***Salvadora persica* (Dried Leaves)**

Phytochemical Constituents and Traditional Uses: *Salvadora persica* (*Miswak*), commonly used as a traditional oral hygiene tool, contains bioactive compounds such as salvadorine, flavonoids, and alkaloids, which are known for their anti-inflammatory and antimicrobial properties (45).

Antitussive Activity: A study conducted by Almas et al. (2017) tested the aqueous extract of *Salvadora persica* in the citric acid-induced cough model in guinea pigs. The results showed a significant reduction in cough episodes, likely due to its anti-inflammatory action, which reduces irritation in the airways. The fruit of *Salvadora persica* are believed to play a role in modulating the cough reflex (46).

***Glycyrrhiza glabra* (Dried Roots)**

Phytochemical Constituents and Traditional Uses: *Glycyrrhiza glabra* (Licorice) is a widely researched herb, known for its sweet taste due to glycyrrhizin. It has been used in traditional medicine for respiratory conditions like asthma, bronchitis, and cough (47).

Antitussive Activity: Studies have highlighted the cough-suppressing potential of *Glycyrrhiza glabra* in preclinical models. A study by Wang et al. (2019) demonstrated that the extract of *Glycyrrhiza glabra* significantly reduced cough frequency in guinea pigs in a dose-dependent manner using the citric acid-induced cough model. The glycyrrhizionoid content were believed to contribute to its antitussive and expectorant properties by soothing the airways and reducing mucus secretion (48).

***Andrographis paniculata* (Dried Leaves)**

Phytochemical Constituents and Traditional Uses: *Andrographis paniculata* (*Kalmegh*) is known for its strong bitter taste and is widely used for its immunomodulatory, antiviral, and anti-inflammatory effects. The main bioactive compound is andrographolide (49).

Antitussive Activity: A study by Liu et al. (2018) investigated the antitussive effects of Andrographis paniculata in guinea pigs using the citric acid-induced cough model. The study reported a significant decrease in cough reflex and airway resistance, which was attributed to the anti-inflammatory and immunomodulatory effects of andrographolide. The study also highlights role in managing respiratory infections that contribute to cough (50).

***Ocimum tenuiflorum* (Dried Leaves)**

Phytochemical Constituents and Traditional Uses: *Ocimum tenuiflorum* (*Tulsi* or Holy Basil) is a sacred plant in Ayurvedic medicine, known for its broad spectrum of medicinal properties, including antitussive, antimicrobial, and anti-inflammatory effects. Its essential oils, such as eugenol, play a crucial role in its pharmacological activities (51).

Antitussive Activity: The antitussive activity of *Ocimum tenuiflorum* was demonstrated in a study by Khan et al. (2018), where the extract was evaluated using the citric acid-induced cough model in guinea pigs. The study showed a significant reduction in cough episodes, with eugenol being identified as a key compound responsible for the cough-suppressing effects. Additionally, the herb's expectorties helped clear mucus, further enhancing its antitussive potential (52).

Conclusion

The review on the pharmacodynamic evaluation of the polyherbal formulation comprising *Curcuma zedoaria* Rosc. (dried rhizomes)*, Salvadora persica* (dried leaves)*, Glycyrrhiza glabra* (dried roots), *Andrographis paniculata* (dried leaves), *and Ocimum tenuiflorum* (dried leaves) highlights the potential of this formulation in managing cough. The formulation's efficacy was tested using a citric acid-induced cough model in guinea pigs, demonstrating significant antitussive activity. Each herb contributes unique pharmacological properties: anti-inflammatory effects from *Curcuma zedoaria* and *Andrographis paniculata*, antimicrobial properties from *Salvadora persica,* expectorant and soothing effects from *Glycyrrhiza glabra,* and bronchodilatory actions from O*cimum tenuiflorum*. These properties collectively address various aspects of cough pathophysiology, including inflammation, mucus production, and airway irritation. This review underscores the importance of integrating traditional knowledge with modern pharmacological evaluation to develop effective and holistic therapeutic solutions.

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