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Review Article

COMPREHENSIVE REVIEW ON POLYHERBAL GEL FOR ENHANCED ANTIMICROBIAL EFFICACY

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ABSTRACT

Herbal medicines widely improved for primary health care because of better cultural acceptability and better compatibility with human body and lesser side effects. Topical drug delivery systems are gaining increased in popularity, and several drugs have been successfully delivered by this route for both local and systemic action. Gels have better potential as a vehicle to administer drug topically in comparison to the ointment because they are non-sticky, requires low energy during formulation. This review gives comprehensive idea of using gerbil medicine for treating microbial infection, concept of polyherbal gel along with its formulation and evaluation approaches and short summary of previously developed polyherbal gel used for antimicrobial activity.

Keywords: Herbal medicine, Medicinal plants, Polyherbal gel, Antimicrobial activity

INTRODUCTION

When Sir Alexander Fleming discovered penicillin 80 years ago, antibiotics were known. Antibiotics have been a comfort to us for many years, up until the discovery of drug-resistant bacteria. Conventional antibiotics, such penicillin and methicillin, were ineffective against resistant bacteria at the outset of antibiotic resistance evolution. Strains resistant to linezolid and vancomycin have now surfaced. Due to the constant need for new antibiotics, physicians are faced with the difficult decision of whether to test a novel multi-resistant strain of an antibiotic or not. Drug resistance posed a growing threat to synthetic antimicrobial drugs like salicylate, chlorhexidine, isothiazolinones, thiosemicarbazones, octenidine, and even quaternary ammonium compounds (Aoki *et al*., 2012; Malmsten, 2011).

It is generally acknowledged that antibiotics and antibiotic-resistant genes have dual roles in influencing the architecture of microbial communities, in line with the Darwinian theory of antibiotics. Antibiotic resistance is now understood to be bacteria's unique reaction to an antibiotic damage, meaning that even with the development of novel antibiotic agents, it cannot be completely prevented. The selection of antibacterial agents is made more difficult by rising rates of antibiotic resistance, medication allergies, and antibiotic shortages. Traditional antimicrobial agents encountered issues with cytotoxicity, overdose, and drug resistance. An effective and secure medication release delivery system is desperately needed to address these issues. This method can postpone the release of harmful antimicrobial drugs and lower the

likelihood of bacterial drug resistance (Martinez et al., 2009; Yang *et al*., 2018)

Just two factors motivate the careful planning of in vitro and in vivo experiments aimed at determining the antibacterial activity of plants: the growth of bacteria, viruses, or parasites resistant to different medications, as well as the toxicity of synthetic pharmaceuticals. There are so many undiscovered aspects of the plant's medicinal potential that there may be evidence of both novel plant applications and hidden mechanisms of action concealed beneath these undiscovered aspects (Tadesse *et al*., 2017).

Traditional medicine has traditionally employed a variety of medicinal plants to treat infectious disorders. Medicinal plants and enigmatic spells are frequently combined by traditional healers; their trade secrets and hereditary recipes are passed down along with the recipes. When it came to ancient medicinal methods, the information was transmitted orally and included intricate protocols for gathering plants, preparing them, applying them, calculating dosages, and connecting them to other unspoken myths about the origin of disease (Ionescu, 2017).

A screening of medicinal plants' chemical compositions showed that they include a variety of bioactive substances, such as alkaloids, tannins, and saponins. Antioxidants, neuropharmacological agents, immunity-potentiating agents, detoxifying agents, and anticancer agents are the primary functional classes of phytochemicals having therapeutic promise. Numerous molecules with variable potencies and occasionally multiple functions make up each of the phytochemicals' functional classes (Singh *et al*., 2015; Akinpelu *et al*., 2015).

Plants generate a diverse range of phytochemicals that often fit into pre-existing metabolic patterns. Triterpenoids, one type of bioactive chemical, have anti-inflammatory characteristics, whereas tannins have astringent, anti-inflammatory, and antibacterial activities. Medicinal properties of saponins include expectorants, blood cleaners, and antibiotics. Furthermore, glycosides are well known for their capacity to raise the forces of systolic concentration, and alkaloids have a notable impact on the central nervous system (CNS). (Olaitan *et al*., 2013; Ugboko *et al*., 2020)

Computational chemists have built a number of libraries for natural products with the goal of offering top-notch resources for natural product screening and selection. Thankfully, a variety of databases have been created with the intention of assessing ethnopharmacology records in silico. Chemoinformatics is utilizing the wide variety of phytochemicals, which ultimately speeds up the drug discovery process (Baxevanis and Bateman, 2013). This link will take you to several more drug development databases. Molecular docking-based in silico High-throughput Screening (HTS) is widely used to reduce the number of medications for both in vitro and in vivo screening. Therefore, HTS is an effective method for quickly identifying possible medications by screening the greatest number of natural substances (Prachayasittikul *et al*., 2015).

The application of a material to the skin for the goal of treating or curing skin disorders is known as topical medicine delivery. These topical medication delivery techniques are frequently used when other routes of administration are inadequate, such as in cases

of localized fungal infections of the skin. Its deeper penetration of the skin enhances absorption. There is no discernible advantage between topical administration and traditional dosing forms. They are usually considered safer and more effective than conventional formulations due to the bilayer composition and structure. In an effort to maximize the local effects of topical dose forms and minimize their systemic effects, efforts have been made to employ drug carriers that permit the treatment to be appropriately localized or absorbed via the skin. It increases the medication's bioavailability by reducing GI irritation and preventing the liver from metabolizing the drug. Topical medications have effect right away in the area they are applied. Topical drugs such as eye, vaginal, and rectal treatments are delivered locally through the skin (Kaur and Guleri, 2013; Ahmed and Ali, 2016).

Some important class of phytochemicals include

Phenolic acids

Phenolic compounds have strong antibacterial properties that can be greatly increased by functionalization. They also have a flexible framework that enables a wide variety of chemical additions. The antimicrobial activity of substances can be increased and the minimum concentration required can be decreased using synthetic pathways such esterification, phosphorylation, hydroxylation, or enzymatic conjugation. Phenolics can target many sites in bacteria through powerful action mechanisms that interfere with bacterial cell wall construction, DNA replication, or enzyme production. This increases the sensitivity of bacteria to these naturally occurring substance (Hollman, 2001; Lobiuc *et al*., 2023).

Saponins

Natural substances known as saponins are a broad class of molecules that are primarily composed of glycon, a sugar, and aglycon, a nonsugar component, joined by a glyosidic bond. Apoginins, which are also known as the aglycone portion, are connected to one or more glycone moieties, which can be hexoses or pentoses. They can be steroidal (C27) or triterpenoid (C30). The chemical structures of different saponins determine their biological characteristics, including their antiviral, antifungal, antibacterial, and anti-inflammatory effects. Inside the cell, saponins bond to cholesterol to form a saponin-cholesterol complex, which ultimately causes the cells to lyse. By attaching to the outer membrane of bacterial cells, saponins disrupted their permeability (Lasztity *et al*., 1998; Leung *et al*., 1997).

Alkaloids

The only thing that unites alkaloids is the presence of a basic nitrogen atom, which gives them a significant deal of structural variation. While most alkaloids only have one nitrogen atom, others can have as many as five. Alkaloids have been shown to have direct antibacterial and antibiotic-enhancing properties in addition to inhibiting bacterial pathogenicity. It follows that alkaloids with dual direct antibacterial and antivirulence properties, like QS-inhibiting macrolide antibiotics, will have higher in vivo activity than their minimum inhibitory concentrations (MIC) indicate (Cushnie *et al*., 2014). Alkaloids with the ability to suppress bacterial virulence without impairing growth or viability may be developed into antivirulence

medications. One recurrent worry about anti-irulence medications is that their narrow-spectrum action would make empirical use impossible. Therefore, efforts should concentrate on alkaloids expected to have broad-spectrum efficacy, i.e., inhibitors of secretion systems and other virulence components conserved across bacterial species, until real-time diagnostics are more widely available (Rex *et al*., 2018).

Flavonoids

The majority of flavonoids are found naturally coupled with sugar in conjugated form; they can be classified as monoglycosidic, diglycosidic, etc. within a certain class. L-rhamnose, D-glucose, galactose, or arabinose are examples of the carbohydrate units, and the glycosidic bond is typically found at positions 3 or 7. Polyphenolic substances known as flavonoids are found in many vascular plants and can take the form of methylated derivatives, glucosides, and aglycones. Either pyrone (flavones and flavonols) or its dihydro derivative (flavanones and flavan-3-ols) is the six-membered ring condensed with the benzene ring (Pretorius, 2003; Górniak *et al*., 2019).

Tannin

High molecular weight polyphenols, known as tannins, range in molecular weight from 500 to 3,000 kDa. When not oxidized, tannins react with proteins through hydrophobic interactions and/or hydrogen bonds; when oxidized, they transform into quinone, which forms covalent bonds with certain functional groups of proteins, including the sulfidric groups of cysteine and the -amino groups of lysine. They are divided into two categories: hydrolysable and condensed. The latter is the one that is now being researched more because of its potential use as an antibacterial product (Rodrigues *et al.,* 2014; Akiyama *et al*., 2001). The phenolic hydroxyl group on the surface of these molecules is responsible for the tannins' ability to bind to the proteins and adhesins found in mucosal cells. By generating a tannin-protein and/or polysaccharide complex, they operate as a protective covering, limiting the action of microbial enzymes, which promotes the breakdown of the plasma membrane and deprivation of substrates essential for the microbial growth, hence stopping the growth of microorganism (Min *et al*., 2008)

Recent development of novel drug delivery for delivering herbal drug

Products that include one or more herbs, processed herbs, and other phytoconstituents in specific amounts and ratios to provide a variety of advantages, such as those pertaining to nutrition, health, and appearance, are known as herbal formulations. Many techniques, including as extraction, distillation, fractionation, purification, fermentation, and concentration, can be used to create herbal remedies from whole plants, plant parts, or plant fragments (Pagar and Khandbahale, 2019). They include powdered or ground herbal components, tinctures, extracts, essential oils, juices that have been expressed, and processed exudates. The complex structure and wide range of active components in the herbal cure collectively contribute to its increased therapeutic efficacy (Patil *et al*., 2016).

Patients have been receiving prescription drugs for a very long time using a variety of traditional dosage forms, such as suppositories, liquids, aerosols, creams, and ointments, which are used as carriers for

drugs to treat serious conditions or long-term illnesses. The main difficulty with this type of drug delivery, nevertheless, was maintaining a constant plasma drug concentration for an extended period of time within the therapeutic range.

Gel: A semisolid drug delivery system for long term efficacy

When compared to other topical preparations and oral administration, gel formulations are utilized to deliver the drug topically because of their simplicity of application, increased contact time, and minimal adverse effects.

Many physical and chemical gradients are formed on the skin after a gel composition is applied. Among these, the water gradient is crucial for the medication to enter the stratum corneum. There are two ways for a medication to enter the transdermal layer: transdermal and translimbal pathways (Singh *et al*., 2013).

There are two subcategories of transepidermal or trans corneal penetration: intracellular and intercellular penetration. The hydrophilic medication penetrates the immobilized water molecules on the stratum corneum's protein filaments' outer surface during intracellular penetration. The hydrophobic/non-polar medication diffuses and dissolves after intercellular penetration through the lipid matrix embedded in between the protein filaments. Three trans-appendageal routes—hair follicles, sebaceous glands, and sweat glands—can be used to transport drugs. This pathway allows non-polar medications to get through, but fewer than 0.1% of the skin is covered by these appendages. Many herbal medications' failure to reach their intended targets, the need for large drug concentrations to have the desired effects, and their poor absorption and bioavailability all restrict their effectiveness (Shah *et al*., 2012; Barry, 2001).

Gels are a perfect delivery mechanism for herbal medications because of their improved permeability, bioavailability, high drug loading capacity, biocompatibility, and capacity to load both hydrophilic and hydrophobic medicines. In order to fight the need for transdermal medication delivery methods to be improved, targeting gels are of significant importance. Gels are an intelligent drug delivery technology that can be used for a variety of medications with either passive or active permeation. Through the enhanced permeability and retention (EPR) effect, passive diffusion and accumulation are facilitated by passive targeting. Active targeting is the process by which nanogel selectively interacts with specific cells through the gel's surface coating. PolyNIPAM gel has demonstrated good migration throughout the skin's epidermis throughout the range of body temperature (Saroha *et al*., 2013; Alkilani *et al*., 2015)

The release of drug from gels

The release of the drug from gels in the site of the action occurs by following ways:

- Simple diffusion of the drug from the gel
- Degradation of gel
- pH stimulus
- Ionic exchange with the environment
- External energy source

Formulation of the Topical Gels

The powdered polymers (ι)-carrageenan, xanthan gum, and guar gum were mixed with warm deionized water at 75°C. Following the complete dissolution of the polymers, the mixture was taken off the hot plate. With vigorous stirring, the appropriate

concentration of copper and zinc sulfates were dissolved in the transparent gel. After bringing the mixture down to room temperature, paraben concentration was added for preservation.

When HPMC was used as a thickening ingredient in a formulation, the polymer was dissolved while stirring in warm deionized water at 75°C. Until a clear gel developed, the resultant solution was kept at room temperature for a whole night. After completely dissolving, copper sulfate crystals and zinc sulfate crystals were mixed vigorously into the gel. A preservative was included in the mixture in the last strep (Kaur and Guleri, 2013).

Poloxamer was dissolved in cold water and kept for one night at 4°C in a refrigerator. A 1:1 ratio of lecithin to isopropyl myristate was used to prepare the oil phase. To ensure that the lecithin completely dissolved, the liquid was kept overnight at room temperature. The aqueous phase was then immediately supplemented with the active components. Using a vortex mixer, one part oil phase and four parts aqueous phase (poloxamer gel) were combined to create the gel.

Direct dispersion of Kollidon 90F, FlexiThix, and Carbomer 940 was done at room temperature using vigorous agitation in deionized water. The gel's active components were evenly distributed throughout. To neutralize the pH to 6–6.5, triethanolamine was added in order to enable Carbomer 940 to gel (Ahmed and Ali, 2016).

Evaluation of polyherbal gel

Physical appearance: One can visually inspect the created gel formulations using herbal extract to check for phase separation, color, homogeneity, and consistency.

Measurement of pH: With a digital pH meter, the pH of created gel compositions must be ascertained. After dissolving 1 g of gel in 100 ml of distilled water, set it aside for two hours. Each formulation's pH can be measured three times, and average values are computed (Goyal *et al*., 2011)

Spreadability: The device, which consists of a wooden block supplied by a pulley at one end, must be used to determine spreadability. This approach measured spreadability based on the gels' slip and drag properties. On this ground slide, an excess of the gel under investigation (about 2 gm) is put. Next, the gel is positioned between this glass slide and another one that is equipped with a hook and has the same dimensions as a permanent ground slide. To release air and create a consistent layer of gel between the two slides, a one kilogram weighted is placed on top of each slide for five minutes. The excess gel is removed by scraping off the edges. After that, pull is applied to the top plate. After that, an 80 gram pull is applied to the top plate. Note how long it takes the top slide to go 7.5 cm (in seconds) using the string that is fastened to the hook. Better spreadability is indicated by a shorter interval (Mishra *et al*., 2011). Spreadability is calculated using the following formula:

$S = M \times L / T$ Where, S= Spreadability, M= weight in the pan (tied to upper slide), L= Length moved by the slide, T= Time (in sec.)

Rheological Study

The generated gel compositions' viscosity can be measured with the Brookfield viscometer (Brookfield viscometer RVT) equipped with spindle No. 7.

Extrudability: Standard capped collapsible aluminum tubes are filled with gel

compositions and sealed by crimping the end. The tubes' weights were noted. The tubes are clamped after being positioned between two glass slides. After that, the slides are weighted by 500 grams, and the cap is taken off. Weighing is done once the extruded gel has been collected. The extruded gel percentage is determined as follows: >80% extrudability is good, >90% extrudability is great, and >70% extrudability is fair (Dixit *et al*., 2013).

Washability

After applying the formulation to the skin, the length of time that can be spent washing it with water is assessed.

Grittiness:

The polyherbal gel is examined under a light microscope to determine if any significant particle debris was visible. Therefore, it is evident that the gel preparation satisfies the necessary criteria of being devoid of specific material and forming the requisite grittiness for any topical application (Jigar and Jaydeep, 2020).

***In vitro* diffusion study**

Using a cellophane membrane, diffusion experiments of the produced gels can be conducted. A gel sample is placed on a cellophane membrane, and 250 ml of phosphate buffer (pH 7.4) is used as the dissolving media for the diffusion studies, which are conducted at 37 ± 1°. Every one, two, three, four, five, six, seven, and eight hours, five milliliters of each sample are taken out and replaced with an equivalent volume of brand-new dissolving media. After that, the samples are examined for the presence of drugs using phosphate buffer as a blank (Sarukh *et al*., 2019).

Drug content determination

One gram of precisely weighed gel is dissolved in phosphate buffer at a pH of 6.8 to determine the drug content. Following an appropriate dilution, the total phenolic content was measured using spectrophotometry, somewhat modified from the previously described Folin-Ciocalteau method. Using a UV-visible spectrophotometer, the absorbance was measured at 765 nm, and the concentration was calculated to estimate the drug content (Jyothi and Koland, 2016).

Stability study

Stability studies should adhere to ICH recommendations. The prepared gel is placed within foldable tubes and kept for three months at three different temperatures and relative humidity levels: 25±2°C/60±5% RH, 30±2°C/65±5% RH, and 40±2°C/75±5% RH. The appearance, pH, and spreadability of the gel are then examined (Bhramaramba, 2015).

Skin irritation test:

Wistar rats of both sexes, weighing 150–200g on average, with their skin intact, were used. Three days before to the trial, the rat had its hair plucked. The test animal is given prepared gel formulations, whereas the control group receives gel base. For seven days, the animals had daily treatments, and the erythema and edema on their treated skin were observed (Singh and Mittal, 2014).

Challenges and opportunities

The expanding pharmaceutical business can get into a multibillion dollar market using polyherbal gel that is created with herbal medications. Nonetheless, there are still a lot of obstacles to overcome before using herbal medications in clinical studies. Eighty percent of the world's population will largely rely on herbal-based medications to address their

health needs, according to a World Health Organization (WHO) report. People still search for complementary medicine in the form of alternative medicine, even in spite of the business potential of allopathic pharmaceuticals. The substantial shifts in people's social, political, and economic values have significantly reduced the therapeutic application of herbal drugs. Through successful research initiatives, polyherbal gel can greatly assist in the integration of herbal medications into widely applicable clinical practice (Khan *et al*., 2013). Polyherbal gel's intriguing qualities such as its non-immunologic reaction, swelling property in aqueous media, increased drug loading capacity, permeability and particle size, and colloidal stability always present new prospects. The design of the delivery system that responds to the external stimuli factor that regulates the drug release rate at the site of action is made easier by polyherbal gel. This boosts the effectiveness of the herbal medications, allowing them to serve multiple purposes (Badke *et al*., 2011).

CONCLUSION

A flexible platform for enhancing the effects of herbal drugs is polyherbal gel formulation. Polyherbal gel offers numerous options in herbal formulations as a medication carrier because of its flexibility and versatility. Herbal Polyherbal gel might potentially transform the natural substance into a very effective pharmaceutical for treating a range of illnesses, including diabetes, cancer, and skin conditions. PLGA, PEG, chitosan, and other polymers are frequently utilized in the production of cross-linked polyherbal gel. With less adverse effects than oral drug administration, these cross-linked Polyherbal gels show great potential for transdermal drug delivery, which affects patient compliance with herbal medications.

As a result, transdermal administration has greater penetration capacity and improved medication bioavailability. With various herbal compositions, the biocompatible and nontoxic Polyherbal gel can be further altered to provide a variety of medicinal effects. Even though a lot of natural medicines have been created, not all of them are safe; some have unfavorable side effects, are extremely poisonous, or interact negatively with prescription medications. An evaluation of the herbal product's quality is necessary for it to be approved by the current medical system. Product development is hampered by the absence of quality control profiles for phyto components and their formulations. The Indian government launched the department of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy) with the goal of creating a pharmaceutical standard and regulating Ayurvedic products using cutting-edge technologies like nanotechnology. The present pharmaceutical industry's potential lies in polyherbal gel formulations, which can yield the required synergistic impact at low medication concentrations and minimal side effects. In general, the Polyherbal gel product may represent a novel medication delivery strategy with real-world applications in the management of microbial diseases.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

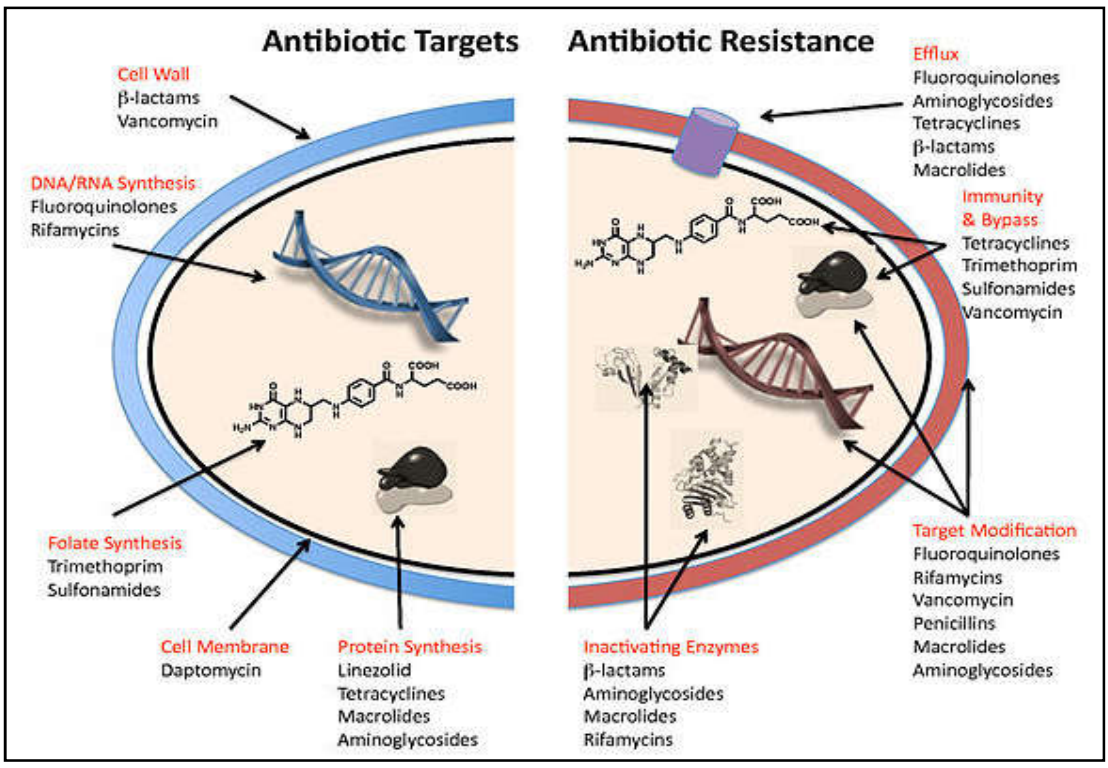

Figure 1: Mechanism action of Antibiotic resistance

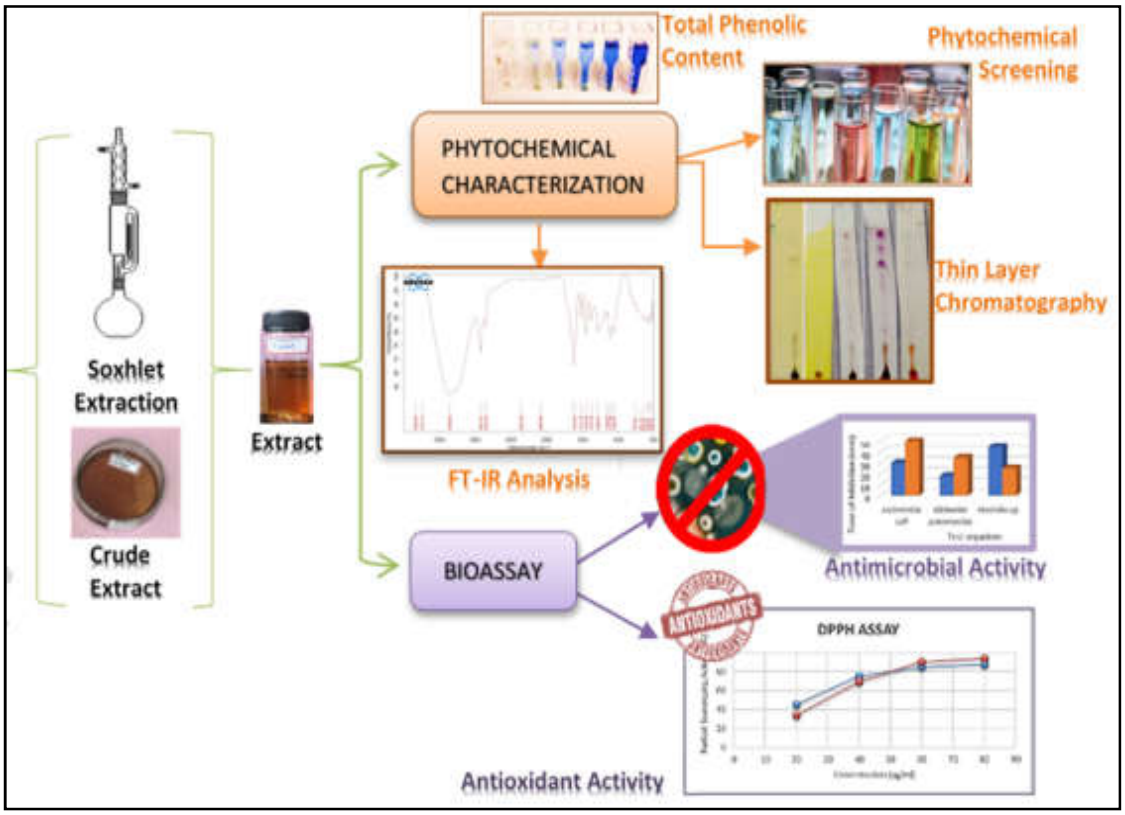

Figure 2: General protocol to screen plant derived compounds

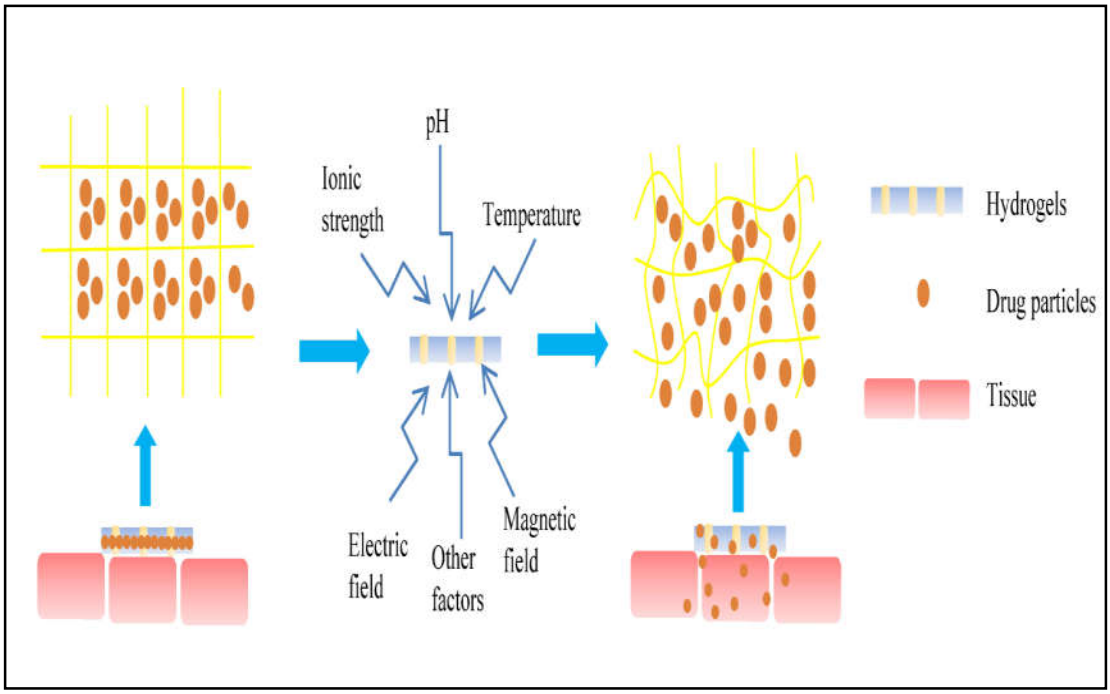

Figure 3: Drug release mechanism from gel

Table 1: Some previously formulated polyherbal gel with antimicrobial effect

Plants used for creating polyherbal gel	Used for	Reference
Azadirachta indica, Curcuma longa, Allium sativum, Ocimum sactum, Cinnamomum zeylanicum nees and *Tamarindus indica*	Topical skin infections	(Bhinge *et al*., 2017)
Azadirachta indica, Salvadora persica and *Calendula officinalis*	Skin infections	(Sohail *et al*., 2022)
Plumbago zeylanica Linn, Datura stramonium Linn and *Argemone mexicana*	Skin infection	(Dev *et al.,* 2019)
Terminalia arjuna, Centella asiatica and *Curcuma longa*	Wound healing and skin infection	(Patel *et al*., 2011)
Boswellia spp., Carum carvi L., Punica granatum L. and Myrtus communis	Treating abnormal vaginal discharge	(Rezghi *et al*., 2019)
Allium sativum, Azadirachta indica, Aloe vera	Treating acne	(Fatima Grace *et al*., 2015)
Cynodon dactylon (L.) Pers, Cassia tora Linn. and *Cassia alata*	Treating skin inflammation	(Dixit *et al*., 2013)
Camellia sinensis, Glycyrrhiza glabra	Treating acne	(Nand *et al*., 2012)
Acacia catechu, Lagerstroemia speciosa, Aegle marmelos, Phyllanthus emblica and *Terminalia chebula*	Microbicide against HIV	(Mishra *et al*., 2019)

Garcinia mangostana and Aloe vera	Treating acne	(Bhaskar *et al*., 2009)
Murraya Koeniggi, Eucalyptus globulus, Dodonaea viscosa and Mentha spicata i	Skin diseases caused by *S. aureus*	(Sharma and Ahuja, 2022)
Dashemani Kandughna	For treating Dandruff	(Dharkar *et al*., 2022)
Zanthoxylum armatum, Glycyrrhiza glabra, Curcuma longa, Vachellia nilotica, Salvadora persica	Tooth infection	(Haque *et al*., 2014)

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