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Exploring the recent Advancement on Allo-Metallic and Herbo-metallic Antifungal agents

Sachinkumar D. Pandey[1]*, Dharmik M Mehta[2]

[1]Department of Pharmaceutics, VIVA Institute of Pharmacy, Virar- 401305 Dist. Palghar, Maharashtra, India.
[2]Department of Pharmaceutics, School of Pharmacy, RK University, Kasturbadham, Rajkot - 360020, Gujarat, India.

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ABSTRACT: Fungal infections are the most common disease. Fungi exist all over, in soil, air, water, creatures and even plants. However, if these fungi invade the human body, they can cause sensitivities, rashes, skin, nail, scalp, palm and foot infections. In more serious cases fungal, infections may lead to lung infections, bloodstream infections, eye infections, brain infections, bone infections and many more. Allopathic drugs such as Clotrimazole, Ketoconazole, Fluconazole etc. were reported to possess amazing antifungal activity but eventually it has developed antifungal resistance and now higher concentration of drugs are required to obtain desired therapeutic action. Herbal formulations including Neem, Thymus vulgaris, Ginger, Turmeric etc. are widely utilized to manage such fungal infections, however, these formulations are usually less potent in comparison to the chemical entities and are active against the specific species of fungi.

In recent years, metal nanoparticles, such as zinc oxide, titanium oxide, silver, zinc, gold, have fascinated great interest of researchers across the world because of plenty of uses in the biomedical field as antioxidants, antimicrobial and antifungal compounds. Various studies have suggested the synergistic effect of nanomaterials in combination of allopathic and herbal drugs. The use of metal colloid or nanomaterials with allopathic drugs may help eventually to overcome drug resistance and concentrated related issues and when used in combination with herbal drugs can make it more effective and broader spectrum. This review describes allo-metallic and herbo-metallic formulations that offer an alternative therapeutic strategy to tackle the problems associated with the existing antifungal agents.

Corresponding author:
Prof. Sachinkumar D. Pandey
Assistant Professor
VIVA Institute of Pharmacy,
Virar- 401305, Palghar, Maharashtar, India.
Tel: +91-9730800591
E. Mail ID: sachinkumarpandey@vivapharmacy.org

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INTRODUCTION:

The fungal kingdom encompasses a diverse array of organisms, primarily manifesting in two fundamental structures: yeasts and moulds. Yeasts, characterized by single, small, oval cells, stand in stark contrast to mould colonies, which comprise filamentous strands known as hyphae. Intriguingly, certain fungi exhibit a dimorphic nature, seamlessly transitioning between yeasts and mould's contingent upon external factors such as

temperature. Remarkably ubiquitous, the majority of fungi thrive effortlessly in their natural habitats, flourishing without the necessity of human or animal substrates. However, some fungi species, notwithstanding, are adventitious pathogens in humans, leading to superficial, subcutaneous or systemic diseases [1]. The clinical impact of fungal infections goes far beyond these devastating demise rates. Fungal infections influence more than one billion individuals every year, of which more than 150 million cases account for extreme and life threatening. Fungal infections, critically, the number of cases proceeds to rise continually [2]. Thus, fungal infections are progressively turning into a worldwide medical issue that is related with high morbidity and death rates as well as with devastating socioeconomic consequences [3]. A crucial component that adds to the rising number of fungal infections is the intense increase of the at-risk population that is specifically vulnerable to Fungal Infections, older individuals, basically sick or immunocompromised patients. The general life expectancy increment because of the accomplishments of present day medication and social advancements, however, the growing numbers of cancer, AIDS and transplantation patients with the corresponding membership of resistant balancing drugs as well as the use of inordinate antibiotic make risk variables and specialties for the advancement of Fungal Infections [4-6]. Among the fungal infections, Candida, Aspergillus, Pneumocystis, and Cryptococcus are the super threatening agents internationally due to the seriousness and higher incidence of the infections [7,8]. Candida spp. is the most isolated yeast among fundamental fungal infections [9,10]. Candida is a genus of eukaryotic fungus comprising 17 species out of 150, which are notable causative agents of candidiasis in people [11]. As per the National Network of Health Security, Candida spp. are the third most widespread causative agent of blood culture infections (15 %) associated with intensive care units, after other normal bacterial microorganisms [12]. *Candida albicans* is the most universal species around the world (50 to 70 %), which produces more infectious illnesses than the total occurrence of infections produced by *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* [9,13]. Aspergillus infections are another principal infection occurring in recipients of hematopoietic stem cell transplants. Around 30 % of people might die from invasive aspergillosis and the remaining 50 % of deaths may occur by candidemia [14]. Cryptococcosis is significantly associated with AIDS and meningitis [15]. This infection typically happens exogenously through breathing or by direct inoculation into the host tissue [16].

The developing resistance of microbes against existing antifungal drugs is one of the fundamental issues among researchers and clinicians. Pathogenic fungi, viruses, bacteria, and protozoa are more challenging to treat with the current medications because of the development of resistance [17,18]. The resistance of pathogenic fungi to existing antibiotics has developed into a worldwide epidemic [19].

The purpose of this work is to review the relevant literature on combination formulation of antifungals especially consisting of metals or ions or colloids with herbal drugs or with allopathic drugs for more efficient and potent antifungal activity than as an individual agent [11].

ANTIFUNGAL AGENTS OVERVIEW:

An antifungal agent is a drug that specifically eliminates fungal pathogens from a host with insignificant harmfulness or minimal toxicity to the host [20].

The various allopathic drugs that are used to overcome fungal infections can be classified as follows;

- Polyene antibiotics : Amphotericin B, nystatin, hamycin.
- Echinocandin antibiotics: Caspofungin acetate, micafungin.
- Heterocyclic compound: Griseofulvin
- Azoles:
- Imidazoles: ketoconazoles, miconazole, clotrimazole.
- Triazoles: fluconazole, itraconazole, voriconazole, posaconazole.
- Allylamine: Terbinafine.
- Antimetabolite: Flucytosine.
- Other topical antifungal agents: Whitfield's ointment, tolnaftate, sodium thiosulphae, selenium sulphide, undecylenic acid, ciclopirox, butenafine [21].

Ketoconazole, fluconazole, voriconazole, itraconazole, posaconazole and ravuconazole are the azoles utilized for systemic fungal infections. These medications act by inhibiting 14 α demethylase, which is responsible for the transformation of lanosterol to ergosterol. Drugs such as Flucytosine acts by blocking nucleic acid synthesis, Griseofulvin acts by disrupting microtubule function.

Caspofungin, nikkomycin acts by inhibiting cell wall synthesis [22].

Other than this modern system of medicines, herbal formulations are also widely utilized to manage such fungal infections. Medicinal plants are of incredible significance for the health of people and communities. Significance of medicinal plants is due to the chemical substances that they produce which has a definite physiological action on the human body.

The most significant of these bioactive compounds include alkaloids, tannins, flavonoids, and phenolic compounds [23]. Pregnane glycosides isolated from Periploca sepium root barks were found to possess strong antifungal activity against various phytopathogenic fungi [24]. Triterpenoids and their Glycosides from *Glinus Oppositifolius* were reported to possess antifungal activities against *Microsporum gypseum* and *Trichophyton rubrum* [25]. At present, the essential oils such as thyme oil which is rich in thymol and carvacrol, tea tree oil rich in terpenes, and peppermint or clove oil are widely being studied for their antifungal activity[26]. Eugenol is the primary antifungal compound of *Ocimum sanctum* i.e Tulsi [27]. Tetranortriterpenoid is the main antifungal compound present in *Azadirachta indica*, commonly known as neem, other compounds present in *A. indica* considered responsible for antifungal activity are 6-deacetylnimbin, azadiradione, nimbin, salannin and epoxyazadiradione [28]. *Foeniculum vulgare* commonly known as fennel has antifungal entities such as, (E)- anethole and fenchone [29]. Spearmint oil and (S)-(-)-carvone are the primary compounds of Mentha spicata [30].

In general, many drugs and herbs are used to treat or cure fungal infections and there is humongous progress made in recent decades in medicine, however, fungal infections are still an irresolvable problem, primarily may be due to the certainty that the available antifungal drugs are of limited potency and effectiveness.

MODE OF ACTION OF ANTIFUNGALS:

The azole antifungal medications act by subduing the combination of the sterol parts of the infectious films and are extremely fungistatic. They repress C-14 α-demethylase (a cytochrome P450 [CYP450] chemical), along these lines hindering the demethylation of lanosterol to ergosterol, the significant sterol of parasitic films. This hindrance disturbs film construction and capacity, which then subdues infectious cell development [31]. The initial imidazole derivatives like miconazole, econazole, and ketoconazole have an intricate mode of action, inhibiting several membrane-bound enzymes and membrane lipid biosynthesis [32]. A pyrimidine- Flucytosine is known to hinder DNA and RNA synthesis in fungi due to its ability to be metabolized to 5-flourouracil that is then subsumed into RNA [33]. Polyenes have extreme affinity for ergosterol present in fungal cell membranes. They combine with it, get embedded into the membrane and several polyene molecules together orient themselves in such a way as to form a 'micropore'. The hydrophilic side structures the inside of the pore through which ions, amino acids and other water-dissolvable substances move out. The micropore is stabilized by membrane sterols which occupy the spaces between the AMB molecules on the lipophilic side constituting the external surface of the pore. Subsequently, cell permeability is markedly increased [34]. Allylamines and thiocarbamates acts as a reversible, noncompetitive inhibition of squalene epoxidase [35] an enzyme, along with (2,3)-oxidosqualene cyclase, is responsible for the cyclization of squalene to lanosterol. The resulting ergosterol depletion and squalene accumulation influences the structure and functions, such as nutrient uptake [36,37].

Plants have been used by humans as medicines for as long as we have existed. Plants are significant to humans. The antifungal activity amongst the plant is by virtue of chemical constituents they contain. Plants are recognized as a rich source of bioactive secondary metabolites of broad variety such as alkaloids, flavonoids, tannins, terpenoids, saponins, and other compounds, which have been reported to have in vitro antifungal properties [38]. The mechanism of action of herbal antifungal drugs, may consist of targeting the biosynthesis of ergosterol, cell wall, and nucleic acid biosynthesis, which may lead to cell death [39].

PROBLEMS ASSOCIATED WITH CONVENTIONAL ANTIFUNGALS:

Fungal infections are a common problem across the globe and Antifungal resistance is a burgeoning threat. The occurrence rate of fungal infections, including resistant infections, has increased during the most recent couple of years, and may be because of deficient or irregular utilization of medications or increased incidence of immunodeficiency states. The increased usage and over the counter availability of antifungal agents in recent years has given rise to the development of resistance to these drugs. The fundamental

biochemical and molecular system that add to antifungal resistance include decreased uptake of the medication, an active transport out of the cell or altered drug metabolic degradation of the cell, alters the interaction of the drug to the target site or other enzymes associated with the same enzymatic process by point mutations, overexpression of the target molecule, overproduction or mutation of the target enzyme, amplification and gene conversion (recombination), and expanded cellular efflux [40].

A few types of fungi are naturally resistant to treatment with specific kinds of antifungal medications. For instance, the drug fluconazole is inactive against infections caused by the fungus Aspergillus, a type of mold. Resistance can likewise develop over the long run when fungi are exposed to antifungal medications. This resistance can occur when antifungal medications are utilized inappropriately to treat debilitated individuals (e.g., when dosages are excessively low, or when treatment courses are not enough), in any event, when antifungal medications are utilized properly [41,42]. Use of fungicides in farming to forestall and treat fungal diseases in crops likewise add to resistance in individuals exposed to those fungicides.

A few examinations have shown that antibiotics which include antifungal drugs may likewise add to antifungal resistance in Candida. This resistance could transpire in an assortment of ways. For instance, antibiotics can reduce good and bad microbes in the stomach, which makes ideal circumstances for Candida growth [43]. It is not known whether diminishing the utilization of all or certain antibiotics can reduce Candida infections, but appropriate utilization of antibiotics and antifungal drugs is one of the main variables in battling drug resistance.

Systemic antifungals are used to treat several fungal infections which are available in various dosage forms such as intravenous agents, oral tablets, oral suspensions, cream, gel, foam, and shampoo. However, Side effects of systemic antifungals may cause several side effects, such as alopecia, chapped lips, skin toxicity including photosensitivity and rashes, photophobia, nausea and vomiting, stomach upset, diarrhea, headache, hypokalemia, peripheral edema, dark-colored urine etc. Sometimes systemic antifungals may result in serious side effects such as photopsia, neurologic toxicity, cardiac toxicity, nephrotoxicity, hepatotoxicity and severe allergic reactions including fever, swollen lymph nodes, skin rashes, swelling of face, throat, or tongue, breathing difficulties and dizziness [2, 44,45].

Herbal drugs or essential oil from herbs are effective naturally without any significant side-effects but are needed in higher concentration in order to achieve desired therapeutic action. Herbal antifungals are generally less potent in comparison to chemical drugs and are active against specific fungal species [46,47]. Besides, oils that are used for therapeutic purposes are supposed to have non-penetrating or low penetration power in skin, which affects its efficacy [48].

METALS AS ANTIFUNGAL:

Metals are fundamental for life and they also have critical roles in fungal homeostasis. Metals are needed for different biochemical processes, generally as enzymatic cofactors. Metals generally perceived for their significance in fungi are zinc, copper, iron, manganese, and silver [49,50]. Owing to the properties of metals, in recent years, metal nanoparticles, such as zinc oxide (ZnO), titanium oxide (TiO_2), silver, zinc, gold, have fascinated great interest particularly with the development of green synthesis method [51,52].

Zinc:

Zinc is a fundamental mineral for physiological and metabolic processes of several tissues and organs, particularly for the immune system. Some inorganic Zinc compounds that were studied are zinc oxide (ZnO), zinc sulphate ($ZnSO_4$) and zinc perchlorate [$Zn(ClO_4)_2$]. In recent years, zinc oxide nanoparticles (ZnO-NPs) also have received special attention due to their interesting physical chemical properties and biological application potential as antimicrobial agents. In later years, zinc oxide nanoparticles (ZnO-NPs) too stand out enough to be noticed because of their interesting physical and chemical properties and biological application [53]. Some forms of Zinc such as Zinc sulfate, Zinc stearate, Zinc oxide, Zinc gluconate, and Zinc chloride are considered as generally recognised as safe (GRAS) (FDA 2022).

Zinc Oxide Nanoparticles probably act by inhibiting the growth of fungi by affecting cellular functions, which causes deformation in fungal hyphae [54]. Zinc Oxide Nanoparticles intervene in wide spectrum antifungal activity through focusing on multiple cellular and molecular mechanisms, which might prevent further acquisition of fungal drug resistance. In comparison, Zinc Oxide Nanoparticles prevented the development of conidiophores and conidia in some fungal species which in due course led to the death of fungal hyphae. ZnO NPs could be used as an effective fungicide in horticultural and food safety applications [54].

Copper:

Copper is a fundamental trace element for virtually all forms of eukaryotic life. Copper has been utilized as an antimicrobial specialist for over a century and is now being added to commercial fungicides [55].Copper is a transition metal and presents itself in oxidation states copper (I), Cu^{+}, and copper(II), Cu^{2+}. Copper and its alloys exhibit amazing properties and the processes include the release of copper ions (electrically charged particles) when microbes, transferred by contact, sneezing or vomiting, land on the copper surface. The ions obstruct cell respiration, punch holes in the bacterial cell membrane or disrupt the viral coat, and annihilate the DNA and RNA inside. This last property is significant as it implies that no mutation can happen – preventing the microbe from developing protection from copper [56].

The Copper Nanoparticles have a potent antifungal activity. Possible antifungal mechanisms of action of metallic copper, copper ions and colloidal copper nanoparticles depend on changes in the structure and function of the fungi cell. Moreover, these particles can influence DNA and disrupt its replication and transcription, which eventually leads to the death of fungal microorganisms [57]. It has also been reported that copper interacts with microorganisms in different ways including cell membrane permeabilization, membrane lipid peroxidation, protein alteration, and denaturation of nucleic acids, eventually resulting in cell death [58].

Silver:

Silver nanoparticles (Ag-NPs) are well known to have inhibitory and fungicidal effects [59,60]. Silver has been utilized for the therapy of treatment of medical ailments for over 100 years because of its natural antifungal properties. Silver nanoparticles restrains duplication and development of those fungi which causes infection, odor, irritation and wounds [61].

Silver nanoparticles (AgNPs) have caught the attention of researchers across the globe because of its broad range of antifungal and antibacterial properties [62]. The silver nanoparticle acts by adversely influencing the cellular metabolism and hindering cell development when it comes in contact with fungus [61]. Silver nanoparticles exhibit potent antifungal effects, probably through destruction of membrane integrity [63]. Silver nanoparticles may also kill fungal spores by destructing the membrane integrity [64]. Silver Nanoparticles might go about as antifungal by causing cell wall disintegration, surface protein damage, nucleic acid damage by production and accumulation of reactive oxygen species (ROS) and free radicals, and blockage of proton pumps [65]. It may act by disrupting the signal transduction pathways of the cells [62].

Gold:

The gold nanoparticles exhibit excellent antifungal activity against the fungus and are incredibly promising for tackling a wide range of biomedical problems [66,67]. Gold Nanoparticles exhibited antifungal activity against *C. glabrata*, *C. albicans*, *C. krusei*, *C. parapsilosis*, and *Cryptococcus neoformans* [68]. Gold Nanoparticles are considered safer in comparison to other inorganic nanoparticles as gold is inert and nontoxic in nature [69]. Presence of Gold (Au) ions in the environment of bacterial cells, and production of radical oxygen are likely the fundamental mechanisms of gold nanoparticles [70].

Iron:

The iron oxide nanoparticles have an extraordinary fascination in biomedical applications because of their non-toxic role in the biological systems. The iron oxide nanoparticles are utilized in biomedical fields for antibacterial, antifungal and anticancer activity [71]. Iron (Fe) is essential for fungal virulence in pathogenic species, as a vital part of iron-sulfur clusters which are required for the activation of nuclear proteins involved in DNA repair [71] and can exist as ferrous (Fe^{2+}) or ferric (Fe^{3+}) iron [72].

Utilizing iron chelators as adjuncts during antifungal treatment might be beneficial, as iron deprivation can alter membrane fluidity and permeability, leading to increased susceptibility to antifungal agents [73]. The calcineurin pathway, engaged in stress response in fungi, is suppressed during iron deprivation, which results into hypersensitivity to stresses, including membrane disturbances, such as those caused by antifungal drugs that target cell membrane homeostasis.

ALLO-METALLIC AND HERBO-METALLIC FORMULATIONS FOR ANTIFUNGAL ACTIVITY:

Metal nanoparticles has great potential to be utilized as nano-fungicides both as an option in contrast to regular fungicides or/and as partners in combating fungicide resistance in terms of effectiveness, potential antimicrobial mechanisms as well as synergy profiles with traditional fungicides [74]. Fluconazole is amongst

the most widely used antifungal medication for the treatment of fungal infections due to its low cost, low toxicity and high efficacy. However, extensive utilization has led to resistance [75,76]. Thus, it is clamount to look for newer and more effective therapeutics [77].

Metal nanoparticles, for example zinc oxide (ZnO), titanium oxide (TiO_2), silver, zinc, gold, have charmed extraordinary interest in recent years. Among these, silver nanoparticles (AgNPs), because of their high microbial toxicity and availability, represent the most prominent one [78]. AgNPs right off the bat showed its antimicrobial impact against different bacteria, like *E. coli*, *E. faecalis* [79,80]. However, recently, AgNPs is reported for its antifungal value alone as well as in combination [81,82]. Silver nanoparticles when conjugated with nystatin (NYT) or fluconazole (FLU) show increased efficacy against *C. albicans* when contrasted with drug alone [83]. The synergistic impact among AgNPs and ketoconazole was reported, in which AgNPs extraordinarily added to the fungicidal activity of ketoconazole [84]. AgNPs when used alone, exhibited no inhibitory impact on biofilm cells, however, the combination with fluconazole caused a significant dose-dependent inhibition on biofilm cells, while no cytotoxic impact was seen on mammal cells [85]. AgNPs and fluconazole combination was tested on a murine model of systemic candidiasis and was found that the combination of AgNPs and fluconazole, demonstrated to be most effective in reducing fungal burden and showed the greatest effect in improving the survival rate of infected mice, which mean that, AgNPs supports amassing of fluconazole in resistant *C. albicans*, and synergize with fluconazole leading to combat fluconazole-resistant *C. albicans* [86]. Silver nanoparticles showed magnificent antifungal action and furthermore improved the antifungal property of fluconazole, this could be utilized as a strong antifungal material [87]. The amphotericin B when combined with silver nanoparticles exhibited enhanced antifungal activity against *Candida albicans* and *Candida tropicalis* most probably because of the synergism between the antifungal activity of amphotericin B and the antimicrobial property of silver [88]. Silver nanoparticles when combined with echinocandin drugs revealed potent synergistic effects against fungi, the result of the same was verified by transmission electron microscopy (TEM) [89].

Gold nanorods loaded with Fluconazole showed low cytotoxicity against human skin cells represented by human dermal fibroblasts. Gold nanorods could be considered a guaranteed way to enhance the activity of Fluconazole towards topical fungal infections and to deal with its adverse reactions and resistance [90].

The antifungal activity of the copper oxide nanoparticles (CuO NPs) along with fluconazole (fluconazole–CuO NPs) was studied against C. albicans and outcomes propose that fluconazole-CuO NPs can give an expected elective treatment to C. albicans infections [91]. Copper (II) and Zinc(II) complexes derived from ketoconazole (KTZ) or clotrimazole (CTZ) when tested against the pathogenic fungi such as *C. albicans*, *C. neoformans*, and *S. brasiliensis* were found to be better than free azoles, confirming that the increase in ligand activity is caused because of the combined use of the metal-drug synergism. Zinc-Ketoconazole complex displayed promising antifungal activities making them potential candidates for the development of an alternative drug to treat mycoses [92]. Zinc oxide Nanoparticles in combination with other antifungal drugs might lead to a reduction in standard doses for desired antifungal activity, expenses of treatment, and drug toxicity [93]. Zinc complexes have synergistic antifungal activity when used along with nystatin [94].

Iron chelation such as lactoferrin, deferiprone, and ciclopirox, when used alone or in combined with antifungal drugs such as azole and polyene against Aspergillus fumigatus was found to enhanced antifungal activity and thus can be used for prevention and treatment of mycosis [95]. Triazole metal complexes when studied for antifungal activity by disc diffusion method against *C. albicans*, *F. oxysporum*, *A. pullulans*, and *A. flavus* was studied and the result was compared with Amphotericin as a standard antifungal drug. It was found that complexes were more active as compared to ligands against all tested fungal strains [96].

Thus, metals show's synergistic effects when used in combination with conventional antifungal drugs. Other than this transition metal complexes when used in combination with plants shows enhanced antifungal activity.

The Silver chloride nanoparticles synthesized from *Malva sylvestris* leaf extracts demonstrated antifungal, antibacterial, antibiofilm potential [97]. The antifungal activity of silver nanoparticles from plant leaves exhibited enhancement in activity due to synergistic effect of silver and essential oil and it was found that synthesized silver nanoparticle from the plant oil was highly active against clinically isolated human fungal

pathogens, *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans*, *Candida tropicalis,* and *Candida kefyr* [98]. Green synthesis of silver nanoparticles using *Zingiber officinale* and Thymus vulgaris extracts exhibits higher Minimum inhibitory concentration in comparison to fluconazole against Candida albicans. Silver Nanoparticles synthesized via thyme extract can be regarded as an appropriate candidate in place of fluconazole to treat the superficial fungal infections due to its lower toxicity and Minimum inhibitory concentration [99]. Growth rates of Candida spp. are restrained in the presence of both Silver nanoparticles and beech bark extract, except for *C. auris*. Silver nanoparticles synthesized with beech bark extract exhibited synergistic activity could serve as an alternative to traditional antifungal treatments [100]. The bioconjugation of Silver nanoparticles with plant extracts reduces their toxicity to biosystems and accordingly improves its effectiveness [101].

The Essential oils extracted from the leaves and seeds of thyme and dill plants restrained *C. nymphaeae* mycelium growth and conidia germination. The inhibitory impact was greatest at the highest Essential oils concentration tested. Encapsulation of thyme and dill Essential oils increased conidia restraint in thyme and dill. Encapsulation of thyme and dill essential oils with copper nanoparticles damage and restrain *Colletotrichum nymphaeae* [102]. The eco-friendly copper oxide nanoparticles synthesised using *Cissus quadrangularis* (*C. quadrangularis*) plant extract was studied against *Aspergillus niger*, *Aspergillus flavus* and it was found that the eco-friendly synthesized copper oxide nanoparticles exhibit better results in comparison to the standard Carbendazim [103]. Curcumin-silver nanoparticles showed a superior antifungal action contrasted with curcumin and silver nitrate solution. *Candida glabrata* and *Candida albicans* were the most repressed and *Candida tropicalis* was the most unrestrained species. Other Candida species under the study were also restrained. Inhibitory activity was dose dependent and it increased with concentration [104]. The natural antifungal plants for example *Azadirachta indica*, *Cassia alata*, *Vitex negundo* and *Neriun oleander* were showed synergistic impact with transition metal ferrocyanides. The natural antifungal plant extracts with metal ferrocyanides complexes were found to be having more antifungal properties in contrast with metal ferrocyanides and plants extracted alone [105].

CONCLUSION:

Metals such as silver, zinc, copper, iron have potential applications in the healthcare system and have an excellent and effective antifungal effect. The unique physical and chemical properties of metals like silver, zinc, copper nanoparticles increase the efficacy in combination. Though there are many mechanisms attributed to the antifungal activity exhibited by metals, the actual and most reliable mechanism is not fully understood or cannot be generalized as the metals are found to act on different organisms in different ways. The findings of this study conclude that the conjugated nanoparticles with conventional medication could be used as efficient antifungal agents and drug delivery vehicles. This can emerge as the solution for preventing resistance by the fungal species. Combination of metals with various allopathic and herbal drugs is possible and it can contribute to the global problem of the emergence of resistance and overcome the limitations, namely, toxicity and health-care costs. Synergistic effect can be obtained when any other drug is used along with metal colloids or nanoparticles. Moreover, allopathic and herbal formulations are potentiated when used in combination with metals which serve as an effective, cost efficient, broad spectrum antifungal with fewer dose limiting side effects resulting in potent antifungal activity in comparison to their individual use. Thus, there is need for further study and research to develop some safe, effective and novel antifungal formulation which includes metal with herbal and or allopathic medicament.

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