

### EFFICACY OF MEDICINAL PLANTS AGAINST FUNGAL DISEASES: A SCOPING REVIEW

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#### ABSTRACT

Fungi can cause detrimental maladies in plants, animals and humans. Concomitant utilization of antimicrobial agents is causing resistance to currently available antifungal drugs and created selective pressure. The need for alternative antifungal drugs is urgently needed due to emerging resistance of fungal strains, high cost of antifungal drugs and numerous adverse effects. Natural products such as plants have been evaluated for their medicinal properties against numerous fungal diseases. The medicinal plants are our heritage and their use for the treatment of diseases has developed the philosophy of herbal medicine. The purpose of this study was to determine the potential effects of medicinal plants used against fungal diseases. This study uses a systemic review and meta-analysis of a compendium of ethnobotanical studies with a medicinal plant constituents against fungal species. The results showed that Ziziphus spina-christi L. Achillea millefolium, Mentha piperita, Rhoicissus species, Hypericum scabrum, Terminalia chebula, Schinus terebinthifolius, Xanthium strumarium L., Polyscias fulva, Zanthoxylum species, Rubus ulmifolius, Boesenbergia pandurata, Piper ovatum Vahl, Syzygium species and Micromeria silicica had antifungal effects of Candida species. Syzygium species is considered to have the highest antifungal effects on Trichophyton, Microsporum, Rhizopus, Candida, Cryptococcus, Aspergillus, Epidermophyton, Scopulariopsis and Botrytis species. Due to increasing challenges with antifungal drugs resistance, these findings suggest that the Syzygium species showed good antifungal effects on nine (9) different fungal species including Candida species. Apparently, Syzygium species might be attributed to some potent form of in vitro antifungal activity, presence of polyphenol and bioactive compounds, control of pathogenicity and aggressiveness against wide range of pathogenic fungi. Candida species is a leading cause of nosocomial infections and patients may die as a result of infection. High burden of fungal infections is increasing annually. Evaluation of medicinal plants as a potential source of antifungal drugs can help expand treatment options in endemic regions.



Keywords: Fungi, antifungal drugs, medicinal plants, *Candida* species and *Syzygium* species.

#### **INTRODUCTION**

Fungal diseases are serious public health challenge in tropical countries (Aliyu *et al.*, 2022). Despite the myriad of antifungal drugs available, the situation is aggravating due to nascent drug resistance. Antifungal resistance is a major problem recently due to the ubiquitous misuse, diagnosis and cost of the drugs (Bishnu *et al.*, 2020). This is due to the persistent use of antibiotics, immunosuppressive treatments, and prolonged survival of immunocompromised individuals (Ghulam *et al.*, 2015). Clinically, antifungal agents used to treat fungal ailments include allylamines, griseofulvin, flucytosine, fluconazole echinocandins, ketoconazole and itraconazole. These antifungal molecules act on mammalian cells which often resulted to adverse drug interactions and toxicity (Ghulam *et al.*, 2015). Common adverse effects of antifungal drugs include itching, poor efficacy in immunocompromised patients, toxicity, nausea, slow therapeutic response and abdominal pain. A potential strategy for finding new molecules to combat the issue of antifungal drugs resistance would be to test the medicinal plants used to treat fungal diseases in traditional methods of treating infections, since medicinal plants have been evaluated as a source of numerous pharmaceutical drugs for a range of fungal diseases (El-Shahir *et al.*, 2022).

Medicinal plants usually synthesized various biochemical compounds and chemicals against fungal diseases. Significant biological activity and phytochemicals have been discovered in medicinal plants many years ago (Rusol *et al.*, 2021). Evaluation of pharmacological and phytochemical properties and activities of various medicinal plants remain unexploited scientific research to outline the efficacy and safety of the plant extracts. Bioactive compounds found in medicinal plants include flavonoids, alkaloids, glycosides, terpenes, tannins and polyphenols (El-Shahir *et al.*, 2022). The beneficial health effects of flavonoids include antithrombotic, antiviral, antioxidant, anticarcinogenic, anti-inflammatory,



antiallergic and hepatoprotective. Alkaloids health benefit effects include anti-tumor and antihypertensive and based drugs effects include amblyopia, caffeine, quinine, cholchicine, nicotine and artemisinin (Awuchi, 2017).

Tannins beneficial effects include geraniin and corilagin usually show anti-human immunodeficiency syndrome activity by inhibiting reverse transcriptase (Ghulam et al., 2015; Rusol et al., 2021). Medicinal plants are often used as culinary herbs and spices in medical and fungal food spoilage contents (Awuchi, 2017). Medicinal plants such as Paris polyphylla, Ampelocissus tomentosa and Dichrocephala integrifolia were evaluated to inhibit significant growth of fungal species. It was evaluated that Terminalia chebula, Sapindus mukorossi, Dicrocephala integrifolia, Boerhavia diffusa, Ampelocissus tomentosa, Rhododendron arboreum, Justicia adhatoda, and Clerodendrum serratum were active against many fungal pathogens at concentrations of 1000 µg/mL (Bishnu et al., 2020). Most of the plant extracts from D. integrifolia and S. mukorossi rapidly lost their activity due to low potency, colored agents or concentrations of potent molecules that superpose with spectrophotometric endpoints at high volumes. However, J. adhatoda, A. tomentosa, R. arboretum, and Aleuritopteris anceps have showed high antimicrobial activity against various microbial pathogens. Ethnopharmacological selection and evaluating range of fungal pathogens is more significant way of examining new bioactive compounds than assessing randomly selected medicinal plants.

#### METHODOLOGY

This research work follow the steps proposed by Moher *et al.* (2009) and Cooper (2009) through selecting and evaluating the sources of information, integrating and analyzing the results of the studies. And follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommended by PRISMA.



#### Selecting the Sources of Information

A search for studies that comprises the medicinal plant knowledge, medicinal plants, fungal pathogens, resistance remedy for fungal infections and ethnobotanical remedy against fungal diseases from October 2021 to April 2022 was conducted in databases that include indexed journals, journals that publish ethnobotanical studies and the studies cited in each of the articles selected for this study were also searched again. In the search for information, only English keywords were used. The databases evaluated were Science Direct, Scielo, Web of Science, Scopus and the publications from all years included in the databases were evaluated. In the article search, the following keywords were used: medicinal plants AND fungal diseases, ethnobotanical AND Antifungal, ethnobotany AND fungal pathogens, ethnomedicine AND Fungal infections, traditional medicinal systems AND fungi, ethnopharmacology AND antifungal resistance, and local knowledge AND medicinal plants.

#### **Statistical Analysis**

The statistical analyses of medicinal plants used against fungal species were evaluated using SPSS version 25.0.

#### **RESULTS**

#### Frequency of Medicinal Plants used against different fungal species

Of the 106 articles reviewed, only 67 are reviewed systemically based on the potential medicinal plants used concomitantly against fungal diseases. Table 1 reveals the results of the antifungal activity from the literature reviewed. Figure 1 showed the rate of occurrence of fungal species obtained from the result of table 1. The results shows that *Candida* species had the highest frequency percentage of 24.59% (15.00) while *Malassezia*, *Rhizopus*, *Scopulariopsis*, *Botrytis*, *Penicillium*, *Colletotrichum*, *Macrophomina*, *Saccharomyces*, *Polyspndylium*, *Pyriculerie*, *Glorosprium*, *Phytophthora* and *Megnaporthe* species had the lowest frequency percentage of 1.64% (1.00). Figure 2 showed the rate of occurrence of



medicinal plants used against different fungal species from table 1. The results shows that *Syzygium* species had the highest frequency percentage of 14.75% (9.00) while *Achillea millefolium*, *Schinu terebinthifolius*, *Rubus ulmifolius*, *Piper ovatum* Vahl and *Micromeria silicica* had the lowest frequency percentage of 1.64% (1.00).

S/N	<b>Medicinal Plants</b>	Antifungal Activity	References
1.	Ziziphus spina-christi	Trichophyton, Microsporum, Aspergillus,	El-Shahir et al., 2022
	L.	Candida and Alternaria species	
2.	Cymbopogon citratus	Aspergillus and Malassezia species	Ignace et al., 2022;
			Carmo et al., 2013
3.	Achillea millefolium	Candida species	Marcelina et al., 2021
4.	Mentha piperita	Candida and Aspergillus species	Meryem et al., 2021
5.	Albiiza lebbeck	Polyspndylium, Aspergillus, Alternaria and	Rehman et al., 2021
(		Fusarium species	Dube $\alpha = 1, 2021$
6. 7	Rhoicissus species	Saccharomyces and Candida species	Dube <i>et al.</i> , 2021
7.	Hypericum scabrum	Trichophyton and Candida species	Fahed <i>et al.</i> , 2021
8.	Eucalyptus globolus	Fusarium,Pyriculerie,Glorosprium,Phytophthora and Megnaporthe species	Zhou et al., 2021
9.	Terminalia chebula	Candida, Aspergillus, Trichophyton and	Venkatachalam and
		Microsporum species	Chittibabu, 2020
10.	Schinus	Candida species	Abeer et al., 2020
	terebinthifolius	1 I	,
11.	Justicia secunda	Colletotrichum, Fusarium, Alternaria and	Jules et al., 2019
	Vahl	Macrophomina species	
12.	Xanthium	Aspergillus, Fusarium, Penicillium and Candida	Parveen et al., 2017
	strumarium L.	species	
13.	Polyscias fulva	Cryptococcus, Candida, Microsporum,	Njateng et al., 2015
		Trichophyton and Epidermophyton species	
14.	Oxalis corniculata	Aspergillus and Fusarium species	Rehman et al., 2021
15.	Zanthoxylum species	Candida, Cryptococcus and Aspergillus species	Ghulam et al., 2015
16.	Rubus ulmifolius	Candida species	Ghulam et al., 2015
17.	Boesenbergia	Microsporum, Cryptococcus and Candida species	Angus et al., 2014
	pandurata		
18.	Piper ovatum Vahl	Candida species	Silva et al., 2009
19.	Syzygium species	Trichophyton, Microsporum, Rhizopus, Candida,	Ghulam et al., 2015;
		Cryptococcus, Aspergillus, Epidermophyton,	Veeramuthu et al.,
		Scopulariopsis and Botrytis species	2008
20.	Micromeria silicica	Candida Species	Duru et al., 2004

Table 1: Potential medicinal plants u	sed concomitantly against d	ifferent fungal species
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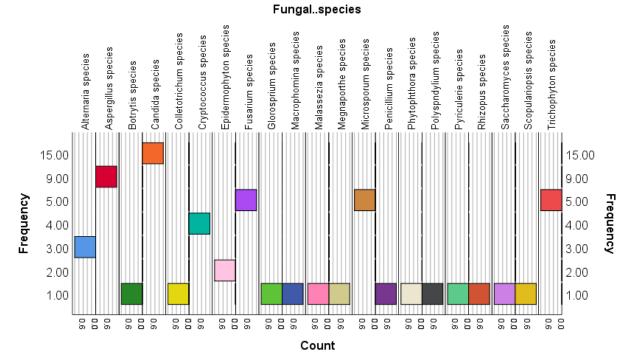


Figure 1: Frequency of fungal species obtained from table 1



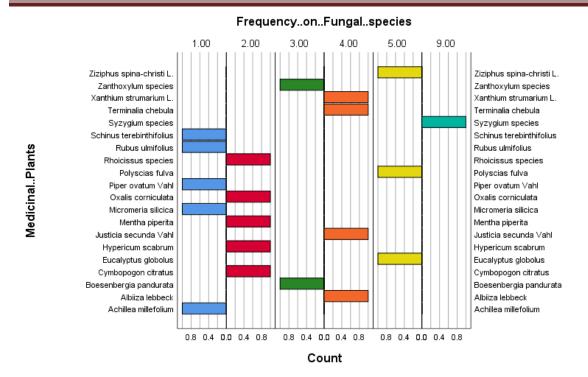


Figure 2: Frequency of medicinal plants used against different fungal species from table 1

#### **Emerging Fungal Pathogens**

Pathogenic fungi caused maladies in plants, animals and human in global population. The superficial infections are usually caused by *Epidermophyton*, *Trichophyton* and *Microsporum* species. Superficial mycosis is one of the most prevalent fungal infections in human as they affect more than 20% of the global population (Rusol *et al.*, 2021). The prevalence of mucosal infections such as vulvovaginal candidiasis affects more than 70% of childbearing age women and approximately 8% of the population suffer from recurrent fungal infections. Fungal species that caused invasive diseases in humans was estimated to kill 1.5 million people annually (Rusol *et al.*, 2021). These life-threatening fungal infections are primarily caused by *Candida*, *Aspergillus*, *Cryptococcus* and *Pneumocystis* species which increasingly cause detrimental infections in individuals with underlying conditions



or impaired immune system. Fungal infections can be subdivided environmentally such as *Aspergillus* species and endogenously such as *Candida* species. *Aspergillus fumigatus* thrives as a saprophyte in most domicile niches such as soil, compost and individual become infected by inhalation of fungal propagules. *Candida albicans* is considered as part of the human microbiota and invasiveness occur from colonizing cells of the individual's gastrointestinal tract. The fungal pathogens have gained the potential ability independently either as colonizers of mucosal surfaces or in a particular domiciles (Rusol *et al.*, 2021).

Fungal pathogens such as Aspergillus species are a major cause of mortality and morbidity in immunosupressed individuals. Aspergillus fumigatus is a common fungal pathogen cause nosocomial fungal pneumonia. Azole drugs were effective against Aspergillus fumigatus but recently it has showed developing a resistance against it (Ghulam et al., 2015). Histoplasma capsulatum latent stage can be reactivated when the patient is immunosupressed and is rare fungal infection in mammals. Fungal infection of the cornea (keratitis) is caused by a rare *Trichophyton* species. Cryptococcus neoformans is the cause of central nervous system mycosis in HIV infected individuals. Candida species has been found to be major cause of nosocomial infections. Candida albicans is the most frequently pathogen isolated from clinical samples and accounts for more than 40% cases of candidiasis (Ghulam et al., 2015; Price et al., 2011). Other emerging fungal pathogens include dematiaceous moulds, Fusarium species and Zygomycetes. Dimorphic fungi include Histoplasma capsulatum, Penicillium marneffei and Coccidioides inmotis.

#### **Traditional Knowledge of Medicinal Plants**

Currently, the knowledge on medicinal plants for treating numerous ailments dates back to the early civilization in the Near East, India and China (Bernard *et al.*, 2020). The use of medicinal plants in human diagnosis, prognosis and treatment of ailments is well documented in many regions of the world (Srivastava, 2018). Essential compounds provided by medicinal plants have a significant impact of medicinal properties in healing human from



various infections (Shakya, 2016). Approximately 60 – 80% of the human population reckon on traditional medicine as for primary healthcare needs in general population (Silveira *et al.*, 2018). Myriad of medicinal plants being approved and recommended for use as herbal medicine is increasing in many regions of Africa and Asia, and gained more recognition due to high cost of medical bills (Bernard *et al.*, 2020).

Basically, medicinal plants knowledge was obtained sequentially via traditional practitioners, elders, herbalists, hunters, spiritualists, ethnic groups and community members written pharmacopoeias and traditional documentation of knowledge for institutions and health care professional. It was evaluated from various dissertations, books, media reports, published work, thesis, inventories and monographs of the diversity of medicinal plants in developing countries (Kigen *et al.*, 2019). There is a high prediction of extensive traditional knowledge of medicinal plant species in Africa due to the significant and utilization of multiple medicinal plant species, beliefs among the different ethnic groups, diversity of cultures and languages in the population. The traditional medicinal plants treated numerous diseases in tropical countries of which elders, healers, herbalists and other community members have knowledge for treating common ailments include diarrhea, typhoid, chest problems and stomachache (Bernard et al., 2020). It was evaluated that there was insufficient knowledge index of medicinal plants by common people based on knowledge of traditional herbalists and healers. Medicinal plants for treatment of pneumonia, malaria, tetanus, and diabetes were examined by more than 40% of the local community members (Bernard et al., 2020). Medicinal plants used for the treatment of meningitis, gout, smallpox, arteriosclerosis, trachoma, rheumatic fever, and arthritis were evaluated by less than 10% of the local community members.

#### **Medicinal Values of Plants**

Current studies on medicinal plants has showed their great pharmacological significant due to the presence of active bio-compounds and medicinal compounds are products of



metabolic pathways. Each plant species has its own genetic structure that constitute the presence of bioactive compounds. Environmental factors also influence the variations in the constituent of phytochemicals molecules present in each plant species (Thomas, 2000). More than 80% of the world population relies on alternative medicines from medicinal plants. More than 70, 000 plants are used in the treatment of diseases worldwide. Indian Ayurveda uses more than 2,000 plants to treat numerous infections. Every medicinal herb constitutes a number of properties that speed up its curative activity. Some common medicinal compounds include vincristine, reserpine and taxol which have been synthesized on a large scale production. The total number of bioactive compounds present in the medicinal plant kingdom is approximately 200, 000 species. The medicinal compounds are used by plants for healing, offense, maintenance, reproduction and defense. Many of these plant species possess antioxidants and polyphenols. Nuts, vegetable and fruits are good source of secondary metabolites (Daniel, 2006). A summary of medicinal plants possessing antifungal properties have been given in table 1.

#### Isolation and Characterization of Antifungal Compounds

The important step for the investigation of therapeutic potential of medicinal plants is preparation of a crude extract and isolation of medicinal compounds. There are numerous number of literature, dissertation and books available regarding medicinal plants which include Phytomedicine: Turning Medicinal Plants into Drugs Modern, Laboratory Handbook for the Fractionation of Natural Extracts and Plant Drug Analysis: A Thin Layer Chromatography Atlas (Ghulam *et al.*, 2015). Most of the books describe the quality, procedures and limitations of reproducibility.

#### **Plant extracts**

The Fresh plant parts such as roots, leaves, flowers, fruits and steams is usually collected. Plants are carefully washed by tap, clean and safe water to remove unwanted contents such as dusts and dried in an oven at 60°C for 8 hours. Dried plants were grinded separately in



an electric pounder machine then powdered plants transferred to a glass sealed bottles and placed in the refrigerator before the extraction process begins (Rusol *et al.*, 2021). In cold water extract, the grinded medicinal plant powder were taken and mixed in measurable distilled water. The dilution of plant extracts was collected into sterilize conical flasks and plugged with sterile cotton then kept in shaking incubator at 200 rpm for 24 to 48 hours. The plants dilution was filtered thoroughly via muslin cloth. This process of filtration was repeated three to five times until a clear aqueous extract of plant was obtained (Rusol *et al.*, 2021). In hot water extract, measured grinded plants was soaked in boiled hot water for about 30 minutes. The plant extract was filtered and evaporated. In alcoholic extract, the same procedure was followed but uses alcoholic solution instead of distilled water.

#### **Preparation plant extracts**

Preparation of the stock solution of aqueous plant extracts by obtained one gram of the grinded plant extracts from any portions of medicinal plant and dissolved in ten milliliters of sterile distilled water, stock the solution in 100 mg/ml dilution and filter using Millipore with a diameter of 0.22  $\mu$ m (Rusol *et al.*, 2021).

#### Bioactive compounds in medicinal plants

Secondary metabolites in medicinal plants such as antioxidants and phenolic compounds are having numerous properties and functions in reproduction, growth and photosynthesis in pharmaceutical industries especially in developed countries. The antioxidant in medicinal plants include phenolic acids and flavonoids which have the potential ability to search for free superoxide radicals, enhance human immunity, anti-aging and reducing the risk of cancer (Wink, 2006).



#### **Uses of Medicinal Plants**

Many years ago, human uses plant extracts as tea due to their special texture and benefit against numerous fungal infections. Significant biological activity and natural compounds are usually found in medicinal plants (Rusol *et al.*, 2021). Among medicinal plants available, the concomitant use of plant roots and stems for the treatment of disease is over 67% compared to bark, flowers, fruits, and bulb being utilized in the primary healthcare system of resource-poor domiciles (Bernard *et al.*, 2020). The insufficient traditional medicinal knowledge in tropical countries depends on the availability of plants which can be established an urgent need to document the data and the knowledge from one generation to another. This can be accomplished by gathering the available data and creating a biological database of medicinal plants for future research, implementation and potential development of new pharmaceutical drugs (Rusol *et al.*, 2021). In herbal medicine, the cynosure on the knowledge of medicinal plants utilized has been increasing gradually in whole world. Many years ago, lessen in cultural diversity has observed negative consequences of human knowledge on techniques of extracting the useful molecules from medicinal plant species, their distribution and management of medicinal plants (Arora, 2008).

#### **Future Prospects**

The significant of medicinal plants against fungal pathogens is increasing annually. More than 80% of the global population relies on medicinal plants and integrated into primary health care settings. There is a need of global forum or consortium to make usage of medicinal plants available and assessable. The regions that are rich in medicinal plants should be focused on and established. This would rise the economy and lead to preparation of indigenous medicines of the poor inhabitants. The discovery of active molecules from medicinal plants with collaboration of developed countries could reduce or eliminate the emerging fungal resistance to the synthetic drugs.



Myriad of years ago, medicinal plants were used to treat human and animal diseases based on the presence of secondary metabolites. Traditional ethnomedical and pharmacological approaches were recently receiving recognition and great attention in modern medicine due to the significant of medicinal plants globally (Venkatachalam and Chittibabu, 2020). In this study, medicinal plants (Syzygium species) have demonstrated antifungal activities on Trichophyton, Microsporum, Rhizopus, Candida, Cryptococcus, Aspergillus, Epidermophyton, Scopulariopsis and Botrytis species, apparently, because of the presence of secondary metabolites such as tannins, coumarin, glycoside, quinone, phenols, anthraquinones, saponins, flavonoids, steroids and other constituents. Syzygium species are very rich in gallic and ellagic acid polyphenol derivatives and also myricetin, kaempferol and acylated flavonol glycosides have been isolated from the medicinal plant species which may be responsible for antifungal activity (Jabeen and Javaid, 2010).

Chandrasekaran and Venkatesalu, (2004) revealed that an aqueous seed extract of *S. cumini* fruit have a potential antifungal activity against *Aspergillus* and *Candida* species which agrees to current study. Polyphenols have essential constituents that are commonly used against numerous insects, herbivores, microorganisms and phenolic compounds of most medicinal plant extracts act as active antifungal agents (El-Shahir *et al.*, 2022). The higher metabolites of gallic and ellagic acid in the plants extract might have a potential ability of antifungal properties. Saima *et al.* (2013) revealed that the presence of tannins such as coffeic acid, catechin, gallic acid and ellagic acid in *Ziziphus* plant extract sample have great medicinal compounds, flavonoids such as rutin and quercetin were assessed of having antioxidant molecules. The combinations of the potential medicinal elements in *Z. spina-christi* plant species were found to be biological functional and possess antioxidant, antibacterial and antifungal properties (El-Shahir *et al.*, 2022). Several studies have confirmed the antifungal activity of *Ziziphus spina-christi* L. *Achillea millefolium, Mentha* 



piperita, Rhoicissus species, Hypericum scabrum, Terminalia chebula, Schinus terebinthifolius, Xanthium strumarium L., Polyscias fulva, Zanthoxylum species, Rubus ulmifolius, Boesenbergia pandurata, Piper ovatum Vahl, Syzygium species and other medicinal plants against numerous pathogenic fungi. Medicinal plants such as *B. pandurata* have demonstrated the ability to develop remedy against opportunistic fungal infections in AIDS patients and can be used to treat several Candida species associated denture stomatitis and help to prevent recurrence of the fungal infection (Agus et al., 2014). S. terebinthifolius shows the antifungal effects against Botrytis species isolated from roses and gerberas (Abeer et al., 2020). The great efficacy of medicinal plants against the pathogenic fungi such as Aspergillus species Trichophyton, Microsporum, Rhizopus, Candida, Cryptococcus, Epidermophyton, Scopulariopsis and Botrytis species was due to the active phytochemical components. This findings supported the studies of Ingnace et al. (2022) and El-Shahir et al. (2022) on the evaluation of antioxidant and antifungal activities of Zizygium and Cymbopogon species leaves and discovered that methanolic leaf extracts had antifungal activity against Aspergillus and Candida species. This study contradicted the findings of Saima et al. (2013) on the results of the antifungal activity of medicinal plant species.

#### CONCLUSIONS

In this study, medical plants were found to be the most potent agents against numerous fungal species especially *Candida* species. This could be attributed to the presence of polyphenol and bioactive compounds of the medicinal plants which can provide promising information for the potential use of their extract in the treatment of fungal diseases. The results of this study suggest the potential use of those medicinal plant extracts as antifungal agents in pharmaceutical company.



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