16 The Effects of Nutraceuticals and Herbal Medicine on *Candida albicans* in Oral Candidiasis: A Comprehensive Review

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Abstract

Candida albicans is part of the healthy flora in the oral cavity. It can also cause opportunistic infection, which can be deleterious. The most typical type of chronic oral candidiasis is denture stomatitis, and *C. albicans* is identified as the most crucial organism in this situation. Due to the development of the resistant form of candida, using conventional drugs can sometimes be ineffective. Herbs and naturally imitative bioactive compounds could become a new source for antimycotic therapy. Several review studies suggest that herbal medicine and natural bioactive compounds have antibacterial, antiviral and antifungal effects. Thus, it is hypothesized that these natural products might have beneficial effects on pathogenic oral fungal flora such as *C. albicans*. Although the effects of herbs have been investigated as antifungal agents in several studies, to the best of our knowledge, the effects of these natural products on *C. albicans* have not yet been reviewed. Thus, the aim of this study was to review the anti-candida activity (especially *C. albicans* in oral candidiasis) of herbal medicines and natural bioactive compounds. It is concluded that, in

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G. E. Barreto, A. Sahebkar (eds.), *Pharmacological Properties of Plant-Derived Natural Products and Implications for Human Health*, Advances in Experimental Medicine and Biology 1308,
https://doi.org/10.1007/978-3-030-64872-5_16

general, medicinal plants and nutraceuticals such as garlic, green tea, propolis, curcumin, licorice root, cinnamon, resveratrol, ginger, and berberine are useful in the treatment of *C. albicans* in oral candidiasis and could be considered as a safe, accessible, and inexpensive management option in an attempt to prevent and treat oral diseases. However, most of the evidence is based on the *in vitro* and animal studies, so more clinical trials are needed.

Keywords

Candida albicans · Oral candidiasis · Nutraceuticals · Herbal medicine

16.1 Introduction

Candida albicans, is the most predominant species found in oral candidiasis, belongs to healthy flora in the oral cavity of human [1–3]. It can convert into opportunistic pathogens due to predisposing factors such as poor oral hygiene, denture instability, systemic factors like immunologic and endocrine disease, medication such as steroids, broad-spectrum antibiotics, immunosuppressors, and various nutritional deficiencies [4]. Some pathogenic mechanism in *C. albicans* transformation phases includes epithelial adherence, production of hydrolytic enzymes, biofilm formation, phenotypic changes, and morphogenesis [5, 6]. Some of the clinical signs of oral candidiasis are thrush and creamy white crude like patches [2, 7].

The typical type of chronic oral candidiasis is denture stomatitis, and *C. albicans* is identified as the most crucial organism in this situation [8]. Some factors, such as poor oral health, instability, loosening of denture, irregularity, and pore of the inner surface of denture, which is considered as a reservoir of microorganism, are attribute to the predisposing factors [8, 9]. Furthermore, in severely compromised HIV patients, oropharyngeal candidiasis is prevalent, and *C. albicans* is the most common pathogen that is isolated from clinical specimens [10]. Difficulty in chewing and swallowing can occur if untreated and can lead to weight loss [7].

Conventional synthetic drugs such as imidazole related compounds (e.g. miconazole, fluconazole) or polyenic derivatives (e.g. nystatin) are used for the treatment of candidiasis [4]. However, drawbacks of these medications include the development of resistant strains or side effects such as bitter taste, allergic reaction, and adrenal insufficiency have necessitated a further search for alternative agents [5, 8].

In this context, herbs and naturally derived bioactive compounds become a new source of antimycotic therapy. Herbal medicine has antioxidants, anti-inflammatory, and antimicrobial properties due to their phytochemical constituents such as flavonoid and alkaloid [2, 11]. Several reviews have indicated that herbal medicine and natural bioactive compounds have antibacterial, antiviral and antifungal effects [12–16]. Thus, it is hypothesized that these natural products might have a beneficial effect on oral fungal flora such as *C. albicans*. Although the effects of herbs have been investigated as antifungal agents in several studies, to the best of our knowledge, the effects these natural products on *C. albicans* have not yet been reviewed. Thus, the aim of this study was to review the anti-candida activities of (especially against *C. albicans*) of herbal medicines and natural bioactive compounds. The methods and findings of reviewed studies are summarized in Tables 16.1, 16.2, 16.3 and 16.4.

16.1.1 Garlic

Garlic (Allium sativum) is one of the herbal medicines with antimicrobial properties, which improves the functioning of the immune system [8]. Garlic contains large amounts of organosulfur compounds, such as allicin and flavonoids, which may prevent oxidative damage and reduce blood pressure and hypercholesterolemia, which might lead to the reduction and prevention of cardiovascular diseases (CVDs) and certain types of cancers [58, 59]. In addition to several health benefits of garlic on chronic diseases, it is

Table 16.1 The effects of nutraceuticals and herbal medicine on *Candida albicans* based on *in vitro* studies

Author, year	*Type of article*	*Agent*	*concentration*	*Way of candida collection*	*Treatment duration*	*Intervention assigned to the control group*	*Type of application*	*Main outcome*
Thamburan et al. 2006 [10]	In vitro	Tulbaghia alliacea Tulbaghia violacea Allium sativum	0.06% 0.15% 0.30%	The culture was obtained from the university	24 h	Fluconazole drug	Aqueous Methanol Chloroform	Extracts of T.violacea were most inferior in preventing the growth of the fungus; they were inactive at the lowest concentration of 0.06% and only shown small zones of inhibition at the higher concentrations. In contrast, all extracts of T.alliacea at all concentrations exhibited antifungal activity
Motsei et al. 2003 [7]	In vitro	Tulbaghia violacea Allium sativum Other species	100 mg/ml	From 5-month-old baby and patient in Christ The King hospital	7 days	Amphotericin B	Aqueous	They had the best activity against candida- Albicans
Mendoza-Juache et al. 2017 [5]	In vitro	Allium sativum	7.8–1000μg/ml	56 patients who wear the denture	48 h	Fluconazole	Essential oil	The essential oil of A. sativum is more effective than fluconazole
Behbehani et al. 2019 [17]	In vitro	EGCG	0.98–62,5μg/ml	Collected from dental patient	48 h	Fluconazole and ketoconazole	Solution	The synergistic effect of EGCG was supported in this study.EGCG alone can inhibit the growth of candida in planktonic and biofilm mode.

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Table 16.1 (continued)

Author, year	*Type of article*	*Agent*	*concentration*	*Way of candida collection*	*Treatment duration*	*Intervention assigned to the control group*	*Type of application*	*Main outcome*
Antunes et al. 2015 [18]	In vitro	Green tea extract	10 ml	Acrylic resin	24 h	Distilled water	Aqueous	Green tea was significantly effective in the heat-cured group but not in microwave one.
Ota et al. 2001 [19]	In vitro/ in vivo	Brazilian propolis	1–10 mg	Dental school patient	48, 72, 96, 120 h	Ethanol	Solution	*C. albicans* was most sensitive strain to propolis, especially at 8 mg/ml
Freires et al. 2016 [20]	In vitro	Brazilian propolis (EEP3, EEP13)	0.2–500μg/ml	Bank of microorganism	24 h	Nystatin	Liquid	Strong antifungal activity was observed, and EEP 13 has a lower MIC than EEP3
Martins et al. 2002 [21]	In vitro	Brazilian propolis (EEP 20%)	20μl	12 HIV-seropositive and seronegative patient	48 h	Nystatin (100 IU) Distilled water (20μl) Fluconazole (25 mg) Clotrimazole (50 mg) Econazol(25 mg)	Solution	In seropositive patient: EEP and nystatin was effective against candida and candida was resistant to other drugs In seronegative patient: Candida was vulnerable to all antifungal drugs and EEP
Gomaa et al. 2013 [22]	In vitro	Egyptian propolis (5%)	25–125 ng/μl	Patient with acute pseudomembranous disease	24 and 48 h	Culture control (no additional drug)	Solution	EEP was successful in preventing candida growth at 75 ng/μl
Fonseca Santos et al. 2019 [23]	In vitro	Curcumin	5 mg/g	School of pharmaceutical sciences	12 h	Curcumin in oleic acid Fluconazole (512μg/ml) Amphotericin B (16μg/ml)	Solution	The formulation was effective in improvement of candidiasis
	Ex-vivo		7.8–1000μg/ml		14 h			Curcumin was more potent than other groups

Mahattanadul et al. 2018 [24]	In vitro	Chitosan-curcumin	0.15	Bioprosthetic biofilm colonization model	10 min + 24 h incubation time	CHX group 0.2 w/v 0.9% normal saline	Mouthwash	Curcumin in addition to chitosan act as a safe agent to the management of candidiasis
Daliri et al. 2019 [25]	In vitro	Curcumin	10.2%	Did not mentioned	30, 60, 120 s PDT time and 24 h incubation time	Positive control: Culture without PS Negative control: Culture without c-albicans Nystatin	Aqueous extract	CUR 10.2% in 30 s has the highest antifungal activity
Seleem et al. 2016 [26]	In vitro/ in vivo	Lichochalcone A (licorice root)	2.8–280μM	Commercial strain ATCC 90028	24 h	Fluconazole (32–320μM) Nystatin (100 mm) Ethanol 1%	Solution	Antifungal activity of Lichochalcone A was comparable to antifungal drugs.
Oliveira et al. 2013 [27]	In vitro	G.glabra L (licorice root)	0.19–11 mg/ml	Obtained from the oral cavity of pulmonary tuberculosis patient	24 h	Untreated group	Solution	G.glabra L shows the highest cytotoxicity effect especially against candida albicnas strain
Roque et al. 2018 [11]	In vitro	G.glabra L (licorice root)	10 mg/ml	Commercial strain ATCC 10231	24 h	Nystatin Glabridin DMSO	Toothpaste Oral gel Oral film	Ethanol extracts showed the highest antifungal activity and oral film with PLGA exhibit the most interaction with mucin
Irani et al. 2010 [28]	In vitro	G.glabra L (licorice root)	4 and 8 mg/disk	Commercial strain ATCC 10231	24 h	Chloramphenicol (30μg) Solvent	Ethanol Aqueous	Leave extracts and ethanolic form had significant antifungal activity
Sharma et al. 2016 [29]	In vitro	G.glabra L (licorice root)	50 g in 67% ethanol	Commercial strain ATCC 66027	24, 48, 72 h	Fluconazol (10 mcg) Itraconazol (10 mcg) Clotrimazol (10 mcg)	Solution	G.glabra L had greatest antifungal activity compared to fluconazole and itraconazole and insignificant activity in comparison with clotrimazole

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Table 16.1 (continued)

Author, year	*Type of article*	*Agent*	*concentration*	*Way of candida collection*	*Treatment duration*	*Intervention assigned to the control group*	*Type of application*	*Main outcome*
Oliveira et al. 2014 [9]	In vitro/ in vivo	C.Z (cinnamon)	2 ppm	Commercial strain ATCC 76485 30 HC acrylic resin	1: 24 h 2: 15 days	2: Artificial saliva Nystatin (100,000 UI/ ML)	1:ESSENTIAL OIL 2:Mouthwash	Cinnamon inhibits the growth of *C. albicans* The hardness of acrylic resins in cinnamon mouthwash influenced less than nystatin group
Taguchi et al. 2010 [30]	Invitro/ invivo	Cassia (cinnamon cassia)	100% (0.2 mg/ml)	Commercial strain TIMM1768	18 h	DMSO 10%	Solution	Strongest effect was related to cinnamon
Latti et al. 2019 [31]	Invitro	Cinnamon	100% (10 mg/ml)	Commercial strain ATCC2091	24 h	DMSO	Crude extract solution	Cinnamon had maximum antifungal activity in comparison with other drugs
Veilleux et al. 2019 [32]	Invitro	Cinnamon Cinnulin pf	1.25–0.195% 62.5–1000μg/ml	Commercial strain ATCC28366 And cases of systemic candidiasis	24 h	Nystatin	Essential oil	Cinnamon oil in combination with cinnulin of can act as an antifungal agent and prevent adhesion of candida to the oral mucosa
Almeida et al. 2016 [33]	In vitro	Cinnamon Citronella	1:7.8–1000μg/ml 2:1 mg/ml	1:Commercial strain ATCC90028 and 2:Human saliva	1:24–48 h 2:Immersion for 3 min and incubation for 24 h	1:Nystatin(0.5–64μg/ml) and fluconazole 2:PBS	Essential oil	Both essential oils exhibited antifungal and antibiofilm activity
Warnke et al. 2009 [34]	In vitro	Cinnamon	Did not mentioned	Commercial strain ATCC10231	18 h	Olive oil Industrial paraffin oil Ethanol 70% H2O2 3% CHX 0.15 Povidone-iodine	Essential oil	The largest effective zone belongs to cinnamon oil.

Lam et al. 2016 [35]	In vitro	Berberine Berberrubine	100μg/ml	Obtain from the American type of culture collection	48 h	Terbnafine DMSO	Solution	BBR in combination with terbinafine will produce larger inhibition zone in plates of *C. albicans*. But BBR or berberrubine alone did not inhibit the growth of *C. albicans*
Wei et al. 2011 [36]	In vitro	Berberine	1.95–250 mg/l	Obtained from the college of dentistry	24 h	Fluconazole (0.5–16 mg/l) Miconazole (0.125–4 mg/l)	Solution	A combination of BBR and miconazole or fluconazole showed strong antifungal activity. However, BBR showed antifungal activity alone.
Quan et al. 2006 [37]	In vitro	Berberine	1–32μg/ml	40 clinical isolated of fluconazole-resistant strains ATCC90028	24 h	ATCC90028 as the control group	Solution	BBR or fluconazole do not show significant Antifungal activity, but the combination of them revealed strong antifungal properties
Zoric et al. 2017 [38]	In vitro	Berberine	5.10.25.50, 100μg/ml	ATCC90028	15 and 60 min	PBS	Solution	BBR showed strong antifungal activity against *C. albicans*
Silva et al. 2016 [39]	In vitro	Berberine	0.125–64μg/ml	Blood sample at central public health	24 h	Other strains of candida used as controls	Solution	BBR showed great antifungal activities.
Aghazadeh et al. 2016 [40]	In vitro	Zingiber officinale(ginger)	0.625–80 mg/ml	Clinical isolate from the Iranian research organization	24 h	No treatment in control Ethanol 70%	Mouthwash	0.625–5 mg/ml can be used successfully in the oral cavity for antibiofilm activity against *C. albicans*.

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Table 16.1 (continued)

Author, year	*Type of article*	*Agent*	*concentration*	*Way of candida collection*	*Treatment duration*	*Intervention assigned to the control group*	*Type of application*	*Main outcome*
Pozzatti et al. 2008 [41]	In vitro	Ginger rhizome	50–3200μg/ml	ATCC0231 HIV positive wit oropharyngeal candidiasis Immunocompromised with disseminated candidiasis ATCC90028	48 h	No additional treatment	Solution	Ginger showed antifungal activity but it was not as potent as oregano, thyme, and cinnamon
Lee et al. 2018 [42]	In vitro	Ginger (gingerol, shogaol)	0–1000μg/ml	DAY185	24 h	DMSO 0.1%	Solution	Ginger showed that antifungal activity in compound contains a smaller carbon side chain
Okamoto-Shibayama et al. 2010 [43]	In vitro	Resveratrol	20–200μg/ml	SC5314	16 h	No additional treatment	Solution	Resveratrol is effective against the yeast form of *C. albicans*
Jung et al. 2007 [44]	In vitro	Resveratrol	10–40μg/ml	Center for academic societies in Japan	48 h	Amphotericin B	Solution	Resveratrol had antifungal activity at a final concentration of 10–20μg/ml
Weber et al. 2011 [45]	In vitro	Resveratrol (R5010)	0.2–2-20μg/ml	ATCC90028 ATCC76615 SC5314	24 h	Fluconazole (0–128μg/ml)	Solution	Resveratrol did not inhibit candida's growth
Juin et al. 2019 [46]	In vitro	Resveratrol (EB487)	0.81–20.32 mM	Atcc28367 Ca14-p	24 h	Untreated group	Solution	Strong ability of EB487 was demonstrated to inhibit biofilm growth and preformed biofilm

Table 16.2 The effects of nutraceuticals and herbal medicine on *Candida albicans* based on clinical trials

Author, year	*Type of article*	*Agent*	*Dose*	*Treatment duration*	*Number of participants*	*Mean age*	*Intervention assigned to the control group*	*Type of application*	*Main outcome*
Bakhshi, et al. 2012 [8]	Randomized double-blind clinical trial	Garlic	40 mg/ml	4 weeks	40	73,52 ± 9.81	Nystatin mouthwash	Aqueous solution	Improving the erythematous lesion
Sabitha et al. 2005 [47]	Randomized clinical trial	Garlic	Quantity sufficient to cover entire lesion	2 weeks	56	More than 18	Clotrimazole solution 1%	Paste	As effective as clotrimazole
Ghorbani et al. 2018 [48]	Clinical trial	Camellia sinensis	0.5%	1 and 7 and 14 days	22	65 ± 11.3	Nystatin suspension 1000 u/ml	Mouthwash	Length and width of lesion decreased in green tea groups as well as nystatin
Pina et al. 2017 [6]	Multicentric randomized trial	Brazilian propolis	2%	2 weeks	40	Over 60 years	Miconazole 20 mg/g	Gel	EEP-AP seems to be no inferior to miconazole and can be recommended as an alternative
Capistrano et al. 2013 [4]	Randomized clinical trial	Brazilian propolis	2% 24%	2 weeks	45	60.76 ± 11.34	Miconazole gel 2%	Gel Mouthwash	Both forms of propolis have antifungal activity similar to miconazole
Santos et al. 2008 [49]	Clinical pilot study	Brazilian propolis	10%	1 week	30	51	Miconazole	Gel	Complete remission of the lesion in both groups was observed
Santos et al. 2005 [50]	Clinical trial	Brazilian propolis	20%	1 week	18	42	Nystatin 100.000 UI/ML	Solution (bottle)	Propolis group treated lesion similar to control group
Ota et al. 2001 [19]	Invitro/invivo	Brazilian propolis	6%	2 weeks	12	–	Hydroalcoholic without propolis	Mouthwash	Propolis group showed a significant reduction in number of candida
Mustafa et al. 2019 [51]	Single center RCT	Curcumin	0.1%	2 weeks	30	58	CHX mouthwash Chitosan 0.5%	Mouthwash	Efficacy of CHI-CUR mouthwash was better than other groups
Oliveira et al. 2014 [9]	Invitro/invivo	C.Z (cinnamon)	625μg/ml	15 days	15	40–60 years	Compared to invitro part of the study	Mouthwash	None of patients showed signs and symptoms anymore

Table 16.3 The effects of nutraceuticals and herbal medicine on *Candida albicans* based on animal studies

Author, year	*Animal type*	*Agent*	*Dose*	*Treatment duration*	*Number of animals*	*Intervention assigned to the control group*	*Type of assessment*	*Main outcome*
Rahayu et al. 2018 [1]	Wistar rats	Camellia sinensis	Green tea 1.25% EGCG 1% EGC 1%	4 and 7 days	35	No additional treatment	Collection of blood serums	Green tea has an immunomodulatory and positive effect against candida more than two other type
Dovigo et al. 2013 [52]	Murine model	Curcumin	7.4, 14.7 and 29.5 mg/ml	20 min preactivation time 7 min LED	45	Positive: DMSO 10% Negative: Animals without immunosuppression	Samples swabbed from the tongue of mice	All curcumin and LED light were able to create a significant reduction in colonies count
Sakima et al. 2018 [53]	Murine model	Curcumin	260μM	5 days	235	No additional treatment	Samples swabbed from the tongue of mice	Cationic CUR-NP ± PDT, NYS1, NYS4, and free CUR+ PDT shows good antifungal activity
Karaman et al. 2011 [54]	BALB/c mice	Curcumin	200 mg/kg	5 days	35	Negative control: Without candida Positive control: Saline solution	Serum sample were assessed	Curcumin in combination with dexamethasone shows significant reduction in candida colonies
Seleem et al. 2016 [26]	BALB/c mice	Licorice	7.5 mM	5 days	15	Nystatin(100 m M) ETHANOL 1%	After euthanizing the mice tongues were sectioned	Lichochalcone A and nystatin show significant antifungal activity
Taguchi et al. 2010 [30]	In vitro/ in vivo	Cassia (cinnamon)	5% 25% 100% (200 mg/ml)	5 times after infection (3, 21, 27, 45, 41 h)	101	No additional control group	Samples swabbed from tongue of mice	100% concentration exhibited antifungal activity and eradicated the symptom

Table 16.4 Summary of review studies regarding the effects of nutraceuticals and herbal medicine on *Candida albicans*

Author, year	Type	Number of included studies	agent	Main outcome
Casaroto et al. 2010 [55]	Review	3 in vitro 2 in vivo	Propolis	Propolis can be suggested for the treatment of candidiasis
Santezi et al. 2018 [56]	Review	Total: 28 Candida-albicans: 7	Curcumin	PDT promote a reduction of c-albicans
Sidhu et al. 2018 [57]	Review	3 animal 3 invitro	Licorice root	Licorice can be mentioned as a useful therapeutic agent and as an alternative drug for oral candidiasis.

revealed that active components of garlic, allicin, and allicetaine (the most sulfur-containing compounds) have a therapeutic and antimicrobial properties [7]. Allicin and garlic extract causes an increase in the synthesis of cytokines, macrophage activity, lymphocytes, and other cells of the immune system [8]. It is effective against gram-positive and gram-negative bacteria, as well as *C. albicans* [7]. Chemical reaction with thiol groups of various enzymes is the significant antimicrobial effect of allicin [8]. Besides, the absorption of allicin and allicetaine through the digestive system and their further entrance in serum and blood could prevent the growth of micro-organisms [8]. Two native South African garlic species are Tulbaghia alliacea and Tulbaghia violacea, which are traditionally used as remedies for a variety of infections and diseases [10]. Regarding the antibacterial properties of garlic, several previous studies have assessed its impact on oral health, particularly *C. albicans*, the main findings of them are reviewed here.

In a randomized, double-blind clinical study, 40 aged people, who wear dentures, were divided into two groups. They were assigned to use garlic aqueous solution at a concentration of 40 mg/ml three times a day for 4 weeks and compared with a control group, in which nystatin mouthwash (medication used to fight fungal infections of the mouth) was used instead of the garlic. Results revealed that the application of nystatin and garlic produced a significant effect on the length and width of erythema. However, garlic aqueous had fewer side effects in comparison with nystatin, so the authors concluded that garlic might be considered as an appropriate replacement for nystatin in handling denture stomatitis [8].

In another randomized clinical trial, 74 patients aged above 18 years were divided into two groups. One group was assigned to use garlic paste (quantity sufficient to cover the entire lesion) with one drop of 2% lignocaine jelly for four times a day for 2 weeks. Another group was asked to use 1% clotrimazole solution. Eighteen patients (7- clotrimazole, 11 garlic paste) did not turn up for clinical evaluation. Results of 56 patients showed that in all, 61.5% of the garlic group showed complete suppression of the lesion compared with 50% of the clotrimazole group. The two treatments did not show statistically significant differences in the response rate [47].

In an *in vitro* study, solvent extractions of different concentrations (0.06%, 0.15%, 0.30%) of Tulbaghia alliacea and Tulbaghia violacea and Allium sativum were prepared, using a solvent of water, methanol, and chloroform. All solutions were tested for antifungal activity against candida-Albicans using agar plate disk. Results showed that extracts of Tulbaghia violacea were weakest in inhibiting the growth of candida. Tulbaghia alliacea and Allium sativum aqueous extracts, at 0.15% and 0.30% concentrations, T. alliacea exhibited a more significant zone of inhibition than A.sativum. In methanol extracts at all concentrations, T.alliacea had a broader area of inhibition. In chloroform extracts, in 0.30% concentration, the most significant zone belonged to the T.alliacea [10]. In an in vitro study, which studied traditional plants for managing candidiasis, they prepared plant material in an aqueous

extract with 100 mg/ml concentration. Then added extracts to sabouraud dextrose agar, which contain *C. albicans*. The aqueous extracts were divided into three parts stored at 4, 23, 33 °C for 7 days to assay antifungal activity. Plants extracts of Allium sativum and Tulbaghia violacea had the best activity against *C. albicans*. Allium sativum and Tulbaghia violacea remained active for 3 and 2 days, respectively, when stored at 4 °C. The Allium sativum extracts were the most stable in solution, although this activity decreased with longer storage [7] In an *in vitro* study, a total of 56 patients aged more than 40 years with acrylic dentures, who wore them at least 6 months, were included. The internal surface of denture was brushed with a sterile swab. Then swabs were suspended and prepared on CHROMagar candida at 36 °C for 2 days and subsequently another additional 7 days in 30 ± 1 °C to ensure reducing false-negative results. The essential oil of A.sativum with a final concentration of 7.8–1000μg/ml was used in this study. The control group was fluconazole with a level of 0.5–128μg/ml. The results of this study shown that the essential oil of A.sativum is more effective than fluconazole in the prevention of the growth of both planktonic and biofilm of *C. albicans* extracts from dentures [5].

16.1.2 Green Tea

Green tea is one of the most popular beverages, which has a high amount of flavonoids with antioxidant properties. Catechins which constitute about 20% of green tea flavonoids are the major constitution of green tea. In addition to several health benefits of green tea and catechins including anti-hypertensive [60], hypolipidemic [61, 62], anti-hyperglycemic [63, 64], anti-arteriosclerotic [65], anti-cancer [66], antioxidant [67], and anti-thrombotic properties [68, 69], green tea (Camellia Sinensis) contains some polyphenolic ingredients which show antifungal activities against Candida species [70, 71]. The potential antimicrobial properties of green tea are getting more prominent in recent decades [48].

Due to anti-inflammatory, antioxidant, anti-mutation, and anti-diabetic properties of green tea, it has an essential role in the improvement of erythema and mucosal inflammation [48]. Green tea contains catechin, which is consist of epicatechin (EC) epigallocatechin (EGC), EC gallate, and EGC gallate (EGCG). EGEC and EGC can influence the proliferation of lymphocyte T and cytokines production; thus, it can be assumed that green tea and its extracts (such as flavonoid) possess immunomodulatory effects against oral candidiasis. Flavonoids can induce synthesis of IL8, IL17, which are chemoattractants resources and can recruit neutrophil for phagocytosis to impede *C. albicans* colony formation [1]. Due to the antifungal activity of green tea, several studies have investigated the potential clinical applications of green tea on the oral cavity [72].

In a randomized clinical study, 22 patients with denture stomatitis were divided into two groups, namely nystatin and green tea. Candida infections of dentures were proved by culturing on CHROMagae candida medium; then patients received nystatin suspension 1000μ/ml and 15 ml green tea mouthwash (0.5%) four times a day. Then lesion size was measured in 1st, 7th, and 14th days. The results showed that the mean of candida colonies showed significant differences in green tea and nystatin groups before and after treatment. The average length and width of the lesion in these two groups decreased with the duration of treatment, and there were no statistically significant differences between nystatin and green tea [48]. In an animal study, which was conducted on 3 months old Wistar rats, monoclonal antibodies (IL8, IL17, HBD-2) were analyzed. Immunocompromised rats (induced by dexamethasone 0.8 mg/kg and tetracycline 12 mg/kg intraperitoneally for 7 days) were divided into seven groups: a control group and the group treated with green tea concentration of 1.25%, EGCG 1%, and EGC 1% for 4 and 7 days separately. Results showed that the expression of IL8, IL17, and HBD2 significantly increased in 7 days relative to 4 days. The expression of antibodies was considerably higher in green tea extracts group compared with EGC and EGCG. Also, there were insignificant differences

between the EGC and EGCG groups [1]. In an *in vitro* study, oral candida samples were collected from dental patients, and after preparation on CHROMagar medium, different concentrations of EGCG and different combination of EGCG and fluconazole or ketoconazole were prepared and added to the well after which incubated for 48 h. The effect of EGCG with or without antifungal drugs was measured in this study to assess the synergistic effect of herbal and chemical drugs. The result was in the following order: EGCG alone showed a significant inhibitory effect on the growth of the colony. It was indicated that the mature biofilms of candida were resistant to fluconazole and ketoconazole. When EGCGA was combined with these drugs, the synergistic effect was observed in the inhibitory effect against Candida species [17]. In another *in vitro* study, the effect of aqueous green tea was compared with free alcoholic mouthwash (Listerine) was analyzed. In this study, 60 specimens of heat-cured (HC) and microwaved cured (MV) acrylic resin were tested. The samples were treated with sabouraud broth and incubated for 24 h in a vertical position due to biofilm formation. After this time, they were immersed in the mouthwash or green tea extract for 15 min. CFU was measured, and results revealed that in HC group, green tea reduced colony formation significantly compared with the control group but in MW group, green tea decreased non-significantly the colony count. In both groups, mouthwash has a significant inhibitory effect on colony formation [18].

16.2 Propolis

Propolis is produced by honey bees from substances extracted from parts of some plants, buds and sap [73]. With regard to a wide range of biological constituents (more than 230 constituents), propolis as a natural resin has several biological activities, including antioxidant, anti-inflammatory, antibacterial, antiviral, fungicidal, hepatoprotective, free radical scavenging, immunomodulatory and anti-diabetic activity [74, 75]. For a long time, propolis was used to improve the health status of numerous diseases, such as mucocutaneous infections of fungal, bacterial and viral etiology and gastrointestinal disorders [76–78]. Along with the antifungal activity of propolis, there is a hypothesis that it may cause a change in the phenotype of the fungus without reducing it quantitatively [4, 6]. Because of this feature of propolis, several investigators have studied the antifungal action of propolis against *C. albicans* [21].

In a multicentric randomized trial, two groups of volunteers, with 20 patients per group, received treatment for denture stomatitis. The control group was treated with an oral gel containing 20 mg/g miconazole and propolis group used a gel with EPP-AP 2%. The treatment follows three times a day for 14 days. The results showed that a significant remission of the lesion during 2 weeks of treatment, and both groups achieved a 70% clinical cure rate. The CFU/ml count was reduced in the miconazole group, but the propolis group, besides its clinical improvement, did not show a significant reduction in the number of colonies [6].

In a randomized clinical trial, 45 patients, who were divided into three groups, were examined because of their denture stomatitis. One group received topical use of miconazole gel 2%, another one, propolis gel 2.5%, and the last one, propolis 24% in the form of mouthwash. The treatment lasts for 2 weeks, and four daily applications were used in these groups. The results presented that there were no statistical differences in efficacy among groups, and clinical remission of stomatitis, wholly or partially, was observed at the end of the treatment [4].

In a clinical pilot study, 30 patients were assigned to use a swab to dry the infected area beneath their complete denture and then apply drugs topically four times a day for 7 days. One group (n = 15) asked to use miconazole gel, and another group was allocated propolis gel. At the end of the week, no significant differences were observed among the two groups. All patients showed complete remission of palatal edema and erythema [49]. In another clinical trial, 18 patients (6 patients in the control group) accept the treatment. In the control group, they were

asked to use the solution of nystatin 100,000 UI/ML four times a day for 1 week. In the other group, they were asked to apply EEP 20% in the same way as used in control one. The results exhibited that all patients treated with EEP and antifungal drugs showed remission of the candidiasis lesions [50].

In an *in vitro/in vivo* study, antifungal activity of propolis was measured. First in the in vitro part, candida species were collected from dental school patients and cultured in M20 agar for 24 h. Then, 1–10 mg/ml of propolis was added to the agar plate and incubated for 48, 72, 96, and 120 h at 37 °C. Results showed that *C. albicans* was the most sensitive strain to propolis at 8 mg/ml concentration. In *in vivo* part, 12 patients, who wear a full denture and show stomatitis, were recruited to the study, five patients received hydroalcoholic solution 6% without propolis twice daily for 2 weeks. The rest of them received the hydroalcoholic solution of propolis (6%) in the form of mouthwash in the same way. Results revealed that all the patients in the propolis group show a significant reduction in the amount of candida in their saliva. However, the control group did not show any differences before and after treatment [19].

In an *in vitro* study, EEP3 and EEP13 were examined. Candida species were obtained from the bank of microorganisms. 0.2–500μg/ml concentration of EEP was added to the medium and incubated at 35 °C for 24 h. The control group was nystatin. In this study, the observation was in the following order: both extracts have vigorous antifungal activity, and EEP13 was stronger than EEP3 [20]. In another *in vitro* study, the effect of EEP on HIV-seropositive and HIV-seronegative with oral candida was evaluated. *C. albicans* were obtained from 12 HIV-positive and 12 normal patients. After culturing candida, EEP 20% applied to the agar surface and incubated at 37 °C for 48 h. The results were compared with the Econazole (25 mg), Clotrimazole (50 mg) and Fluconazole (25 mg). Also, 100 IU nystatin and 20μl sterile distilled water were used as the positive and negative control group, respectively. The results were in the following order: in seronegative patients with denture stomatitis, *C. albicans* showed significant vulnerability to all antifungal and EEP groups. In the seropositive group, clotrimazole and fluconazole did not inhibit the growth of candida. Econazole was ineffective against fungus and EEP, and nystatin, with no significant differences between them, produced a bigger inhibition zone against candida. Candida was significantly susceptible to EEP and nystatin [21].

In another *in vitro* study, Egyptian propolis was assigned to assessed adhesion and germ tube formation of oral candida. Candida species were taken from a patient with acute pseudomembranous and cultured in YPD agar plate. EEP 5% with concentration 25–125 ng/μl added to agar plate and colonies were counted after 24 and 48 h at 37 °C. Results showed that a gradual decrease in CFU occurred at 75 ng/μl, and propolis was successful in preventing germ tube formation [22]. In a review article that analyses phytomedicines for candida-associated denture stomatitis, pointed out that propolis may activate macrophage. Also, it is indicated that gel formulation could be used as an alternative topical choice for the improvement of denture stomatitis [55].

16.3 Curcumin

Curcumin is the bioactive pigment found in turmeric, which is known for its safety and multitude of pharmacological effects [79–88]. Photodynamic therapy (PDT) originates in the interaction between two items: a nontoxic photosensitizer (PS) and visible light. Interaction between these two factors releases reactive oxygen species (ROS) in front of oxygen. ROS are toxic and can destroy microorganisms [25]. Curcumin has excellent potential as a PS due to its ability to be activated by blue light [56]. Also, curcumin possesses antitumor, anti-inflammatory, antioxidant, and antimicrobial features [16, 25]. Regardless of these features, curcumin is lipophilic, so the clinical application of curcumin can be problematic. Numerous research performed to find out a more effective drug delivery system [53] and its potency as a PS, in addition to efficacy against oral candidiasis [51]. In a single-

center randomized clinical trial, 30 patients over 20 years old, who wears removable acrylic dentures and possess denture stomatitis, were divided into three groups. (1) Chitosan-curcuminoid (CHI- curcumin) mouthwash 0.1%, (2) chlorhexidine (CHX) mouthwash, and (3) vehicle formulation comprising chitosan 0.5% and PEG 400 (CHI). They were assigned to use them for 30 s three times a day for 14 days. Results showed that all groups had a high site activity in comparison with before treatment. CHI-curcumin was significantly stronger than other groups, which showed an 80% complete response [51]. In an animal study, which considered photodynamic inactivation of *C. albicans* in a murine model, 45 mice were divided into different groups. The groups are in the following order: one negative control group that contains five mice without any immunosuppression and one positive control group that treated only with sterile saline solution at 10% DMSO. Other groups received 7.4 (20μM), 14.7 (40μM), 29.5 (80μM), mg/l of curcumin with and without LED (455 nm, 89.2 MW/cm2). The last group received an LED light in the absence of curcumin. First of all, in treated groups, curcumin was topically applied to the dorsum of the tongue in a dark room for 20 min and was not swallowed. Then LED was performed for 7 min. The results exhibited that PDT was effective against candida, and all concentrations of curcumin produce a significant reduction in colonies. However, there were trivial differences between 40 and 80μM [52]. In another animal study, PDT by curcumin encapsulated in nanoparticles (curcumin-NPS) was conducted on the murine model, which were immunosuppressed to induce oral candidiasis. Two hundred thirty-five mice were selected in this study. Arrangement of groups was in the following order: the control group that received no treatment, free curcumin with and without PDT, anionic CUR-NP with and without PDT, cationic curcumin-NP with and without PDT. Nystatin (four times a day (NYS4) and once a day (Nys1). The maximum concentration of curcumin was 260μM, and treatment was given daily for 5 days. Results revealed that free curcumin without light and anionic CUR-NP (with and without light) did not show a significant reduction in colonies, whereas other groups decreased colony counts. Free curcumin with PDT was similar to cationic curcumin. There were no differences between NYS1 and NYS4. There were no differences between cationic CUR-NP with or without PDT [53].

In another animal study that analyzes the effect of curcumin on oropharyngeal candidiasis, 35 of BALB/c mice were divided into five groups. Group I received 1 mg/kg dexamethasone, group II has gotten 200 mg/kg curcumin dissolved in 2% carboxymethyl cellulose orally, group III received dexamethasone plus curcumin and group IV and V has gotten saline. Induction of candidiasis and asthma was not performed on group V and the treatment lasted for 5 days. Outcomes showed that groups II and III showed a significant reduction in candidiasis without differences between them. Also, group I indicated a significant lessening, but it was lower than other groups [54].

In the *in vitro/ex vivo* study, the antifungal potential of curcumin was assessed; in the ex-vivo part, retention of curcumin in the mucosa was measured. Experiments were carried out with curcumin, and formulation diluted to 30% with artificial saliva. Results compared to the control group (curcumin dissolved in oleic acid). Outcomes showed that retention values after 12 h in curcumin and formulation 30% were five times and three times higher than control, respectively suggesting that this system can be used for drug delivery. In the invitro part, curcumin with concentration from 7.8 to 1000μg/ml was added to the well and incubated at 37 °C for 48 h. Control groups were amphotericin B (16μg/ml) and fluconazole (512μg/ml). Results revealed that curcumin was more effective than control groups against candida colonies [23].

In the *in vitro/in vivo* study, the efficacy of chitosan-curcumin was evaluated. The *in vivo* study was carried on hamsters and evaluated ulcer healing, which is not the purpose of this review. Nevertheless, in the *in vitro* study, for determination against fungus in biofilm, 0.1% curcumin 0.5% chitosan mouthwash was used and compared to 0.2% CHX, blank formulation,

formulation with 0.5% chitosan only and 0.1% curcumin only. Disks contain candida were soaked in these solutions for 10 min and then incubated for 24 h at 37 °C. Results revealed that when curcumin combined with chitosan, its anti-candida efficacy was comparable to CHX mouthwash [24]. In another *in vitro* study, to assess PDT, an aqueous extract of curcumin 10.2% and methylene blue at 0.1% and 0.2% concentrations were used. Each solution measured with and without PDT and compared to the positive and negative control group, which was a culture without using PS and culture without *C. albicans*, respectively. As well, one group consist of 0.1 ml nystatin was compared. The highest antifungal activity was observed in 10.2% curcumin with 460 nm diode laser (25 MW) for 30 s. furthermore, curcumin was significantly more efficient than nystatin [25]. Recently, a review article determined the effectiveness of PDT on curcumin against several microorganisms and concluded that permanent DNA damage in candida occurred due to PDT. However, further investigations are needed in this aspect [56].

16.4 Licorice Root

Licorice root is composed of flavonoids and triterpenoids [89]. Some bioactive natural compound in licorice root is glycyrrhiza species, glabridin, liquiritin (a glycosidic form of liquiritigenin) and lichochalcone A [11, 29, 89]. These extracts show some antiinflammatory, antiulcer, antimicrobial, and antifungal activities [11]. The effectiveness of licorice root in oral diseases such as dental caries, candidiasis, periodontal disease has been great interest recently [57]. Several studies investigated the effect of licorice root on preventing and treating oral disease [57].

In a study that evaluates the antifungal activity of lichochalcone A against candidiasis, *in vitro* and *in vivo* studies were conducted. In the *in vitro* assay, commercial *C. albicans* strains and some resistant strain to fluconazole were selected. The final concentration of lichochalcone A was 2.8–280μM and used as a test group. Fluconazole (32–320μM) and nystatin (100 mM) used as positive control and 1% v/v ethanol as vehicle control. The drugs were applied to plates of candida and incubated for 24 h at 37 °C. Results demonstrated that in ordinary candida, lichochalcone A shows a comparable antifungal activity in similar potency of antifungal drugs, and in resistant strain, lower concentration of lichochalcone A was required to inhibit the growth of strain [26].

In the *in vivo* part of this study, 15 Balb/c mice were used. They were infected with oral candidiasis. The topical use of lichochalcone A (7.5 mM) for 30 s was applied twice daily for 5 days. Nystatin (100 mM) and ethanol 1% used as positive control and vehicle control, respectively. Mice were euthanized, and the tongue of them was sectioned and evaluated. There was a significant reduction of strains in the lichochalcone A and nystatin group. The tongue of these samples showed less severity of hyphal invasion compare to the vehicle control (39).

In an *in vitro* study, the effect of different herbal drugs such as glycyrrhiza glabra L (G.glabra L) was assessed against candida and bacterial strains. Strains were cultured, and extracts of G.glabra L (0.19–100 mg/ml) were applied on plates and incubated for 24 h at 37 °C and was compared to untreated control culture. It showed that the highest cytotoxicity was related to G.glabra L in contrast to other herbal extracts, and candida species were more sensitive to the extracts than bacterial one [27].

In a further *in vitro* study, bioadhesive nanoformulation of G.glabra L was measured. Different solvents, nanoparticles, and mucoadhesives dosage form were used that are named in the following order: solutions such as ethanol/acetone/dimethyl sulfoxide (DMSO)/water and hydroalcoholic. Nanoparticles (NPS) such as alginate, polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), and NPS that were embedded into toothpaste, oral gel, and oral film. The final concentration of extracts was 10 mg/ml. They were applied on plates of c-albicans and incubated for 24 h at 37 °C. The results were compared with negative control (DMSO) and two positive ones (nystatin and free glabridin). The outcomes from this study showed that the most active extracts were ethanolic one (18%

w/w). NPS was produced successfully, and the antifungal activity of NPS was similar to free extracts of glabridin in MIC. Also, the oral film with PLGA NPs showed the highest interaction with the mucin. Besides, toothpaste with alginate NPs and oral gel with PLA NPs show high interaction with mucin [11].

In another *in vitro* study, different types of G.glabra extracts were examined including leaf ethanolic (5.4%), leaf aqueous (4%), root ethanolic (10%) and root aqueous (9.6%). They were added on c-albicans agar plates in 4 and 8 mg/disk and incubated for 24 h at 37 °C. The outcomes were compared to chloramphenicol (30μg) and solvent disk as the positive and negative control, respectively. Results showed that leaf extracts exhibited better activity than root extracts. As well, ethanolic extracts showed the most antifungal activity [28]. Moreover, an *in vitro* study, which examined antifungal activity of different medicinal plants, showed that extract of G.glabra L had a stronger inhibitory effect against other extracts. In comparison to antifungal agents, G.glabra L had better antifungal activity than fluconazole (10 mcg) and itraconazole (10 mcg) but lesser efficacy than clotrimazole (10 mcg) that was not significant statistically. In their method, they applied extracts (50 g powder dissolved in 67% ethanol) of different plants on plates of c-albicans and incubated for 24–48-72 h. G.glabra L showed maximum efficacy and was the most effective agent among all plants in this study [29]. In a review of studies such as those by Messier et al. (2011) [90], Utsunomiya et al. (2000) [91], Lee et al. (2009) [89] and Fatima et al. (2009) [92], and concluded that licorice is a therapeutic agent and can be used as a substitute agent for oral candidiasis [57].

16.5 Cinnamon

It has been shown that cinnamon possesses antiseptic, antimicrobial, analgesic properties [9]. This feature, especially antifungal activity, may be related to cinnamaldehyde. It inhibits amino acid decarboxylase activity. Cinnamaldehyde makes 50.5% of cinnamon bark and can involve in the biologic process due to its electronegative feature and reacts with the nitrogen-containing compound. This process inhibits the growth of microorganisms [31]. According to these characteristics, several studies have been conducted to displayed numerous beneficial of cinnamon against fungus like candida-albicans. In a study comprising of *in vitro* and *in vivo* assay, essential oil of Cinnamomum zeylanicum (C.Z) against oral candidosis was evaluated. In phase I study (*in vitro*), essential oil at a concentration of 2 ppm used as a solvent and compared to nystatin (control). Oil added to plates of candida and incubated for 24 h at 30 °C. In part II (*in vitro*), thirty HC acrylic resins were divided into three groups of artificial saliva (negative control) mouthwash, C.Z and nystatin. The acrylic resin was immersed for 1 min, three times a day for 15 days. Finally in phase III (clinical) 15 patients who showed signs and symptoms of denture stomatitis, assigned to use mouthwash (C.Z) 3 times a day for about 60 s in 15 days. Additionally, they received a container containing 500 ml of mouthwash to clean dental prostheses [9]. Results of these three phases were in the following order: all the test strains showed sensitivity to essential oil, and c-albicans showed the most sensitive behavior. For acrylic resin, the surface hardness of prosthesis was analyzed, and the mouthwash group causes a lower degree of changes in hardness when compared with the nystatin group. Finally, the clinical phase of the study revealed that using mouthwash at a concentration of 635μg/ml can heal the signs and symptoms [9]. In another study, the effect of Cassia (Cinnamomum cassia) on the murine model and culture of c-albicans was evaluated, In the *in vitro* condition, the effect of different herbs was measured, and cinnamon, DMSO (as control) were compared, too. They were added to the well and incubated for 18 h at 37 °C. Results showed that the inhibitory activity of cassia preparation was relatively stronger than other herbs. In the animal part of the study, 31 mice were examined for the cassia effect and 70 mice for other herbs. Cassia prepared in different concentrations 5% 25% and 100% (200 mg/ml). Control mice received no treatment. This preparation was administered by

force-feeding. Results exhibited that 100% concentration showed a great clinical score in the tongue, whereas 5 and 25% did not [30]. Furthermore, in an *in vitro* study. 100% (10 mg/ml) concentration of different extracts such as cinnamon was added to the standard strain of c-albicans and allowed to stand for 10 min, then incubated for 24 h at 37 °C. the control group was DMSO. Results showed that cinnamon extract showed the highest antifungal activity in comparison with other herbs such as cumin, dried black pepper, dried India bay leaves [31]. In an additional study that examined on antifungal activity of cinnamon bark and adherence to epithelial cells, they used cinnamon oil (1.25–0.195%), cinnulin pf (62,5–1000μg/ml) as test group and nystatin was used as a reference. Summary of the results is in the following order: cinnamon oil showed inhibition of *C. albicans* growth, but cinnulin pf did not have any effect on fungus even at maximum concentration. However, both of them significantly reduced biofilm formation. Also, either of them (cinnulin more than cinnamon oil) reinforcing the epithelial could prevent the invasion of the oral mucosa by oral pathogens. Cinnulin pf meaningfully weakened the adherence of *C. albicans* while no such effect was observed with cinnamon oil. In conclusion, to obtain the best way against the adherence of candida and inhibition of its growth is to combine two cinnamon fraction [32]. In another *in vitro* study, at first, 7.8–1000μg/ml concentration of cinnamon citronella essential oil was compared to nystatin and fluconazole (concentration range of 0.5–65μg/ml). Agents were added to the *C. albicans* culture and incubated for 24–48 h at 37 °C. Secondly, 27 HC acrylic resins were contaminated with human saliva that was collected from two healthy people, and different considerations were performed to allow adherence of candida to the surface of acrylic resins. Three groups of acrylic resin immersed in PBS (control), cinnamon essential oil, and citronella essential oil for 3 min. The results of two parts of the study exhibited that both of the essential oil had an antifungal and antibiofilm activity that can be due to the lipophilic nature of essential oil that disrupts the cell membrane of microorganisms [33].

Moreover, in the *in vitro* study, the activity of Indian medical plants such as Cinnamomum verum bark (C.V) against fluconazole-resistant *C. albicans* was assessed. 250, 500 and 1000μg/ml concentration of plants were prepared and added to the well and incubated for 24 h at 37 °C. The results showed that all extracts, specially C.V, exhibited antimycotic activity and can be used as an alternative drug against *C. albicans* [2]. Finally, another *in vitro* study that investigated the effect of different essential oil against microorganisms discovered the antibacterial and antifungal activity of all essential oil include cinnamon oil. Similarly, it showed that the largest active zone was attributed to cinnamon oil. In this study, their control group was olive oil, industrial paraffin oil, ethanol (70%) H2O2 (3%) CHX (0.1%), and povidone-iodine. Also, their incubation time was 18 h at 37 °C [34].

16.6 Resveratrol

Resveratrol is a major bioactive component in plant extracts that have been used for treating various human diseases as traditional medicine [44]. Some pharmacological effects of resveratrol, such as antiviral, anti-inflammatory, lifespan extension, have been demonstrated in various studies. But little evidence about antifungal activity exists [43]. In an *in vitro* study, 20–200μg/ml stock solution of resveratrol was added to the well of *C. albicans* and incubated for 16 h at 30 °C. To assess the morphological transition of *C. albicans*, they recognized that resveratrol was effective in both types of fungus (hyphal growth and yeast-form growth) and can inhibit *C. albicans* growth. Also, resveratrol impaired morphological transition in various situations. For instance, serum induction, nutrient starvation, and neutral ph. They mentioned that the inhibition of yeast form occurred at 100 or 200μg/ml concentration [43]. Moreover, another *in vitro* study has been indicated that the compound of resveratrol can disrupt the serum-induced fila-

mentous form of *C. albicans*. They stated that potential antifungal activity was at 10–20μg/ml concentration. Nevertheless, it was a little less potent than amphotericin B that used as a control group. They proposed that the antifungal activity of resveratrol is due to the induction of some intracellular physiological changes, Trehalose accumulation happens, and cell-cycle will be arrested [44]. On the contrary, an *in vitro* study that used 0.2, 2, and 20μg/ml solution of resveratrol and compared with fluconazole (0–0.128μg/ml) stated that no distinct reaction observed against *C. albicans* even at 20μg/ml. They incubated the plates with resveratrol and candida for 24 h at 37 °C.in their study, different experimental condition and type of candida strains were mentioned as a variable effect of resveratrol antifungal properties [45]. On the other hand, the latest study in 2019, which investigates the antibiofilm activity of a semi-synthetic molecule obtained from resveratrol, showed antifungal activity of this phytochemical. In this essay, 0.81–20.31 mM concentration of EB487 (resveratrol) was applied to the well and incubated at 37 for 24 h. They concluded that above 8.13 mM would inhibit biofilm growth regardless of the studied strains and 20.32 mM as the highest tested concentration inhibits 80% biofilm growth [46].

16.7 Ginger

Ginger is used to treating movement disorders, nausea, and vomiting during pregnancy in traditional medicine [40]. It consists of polyphenol compounds in its root and extract, which have considerable antioxidant activity. Several studies have shown antibiofilm activity against pathogenic bacteria [41] and antifungal properties against *C. albicans* isolated from the patient with genital candidiasis. However, there are only a few studies evaluating the effect of ginger on oral candidiasis [40]. In an *in vitro* study, the mouthwash form of ginger was applied to the well of candida and incubated for 24 h. different concentration of ginger (0.625–80 mg/ml) was compared to Muller-Hinton agar without ginger extracts and ethanol 70% as control groups. They concluded that biofilm reduction started at a concentration of 0.625 mg/ml, and at 40 mg/ml, no sign of biofilm formation was observed. Indeed, they mentioned that 0.625–5 mg/ml could be used successfully against candida colonization in the oral cavity [40]. In another *in vitro* study, the effect of essential oil of different plants such as cinnamon, ginger rhizome, rosemary, thyme, sage, and basil against *C. albicans* was investigated. *C. albicans* was selected from HIV positive patient that infected by oropharyngeal candidiasis or immunocompromised patient with disseminated fungal infection. Also, commercial strains used in this study as control strains. Candida species divided into two groups namely, fluconazole-susceptible and fluconazole-resistant [41]. The essential oil was prepared with 50–3200μg/ml concentrations applied to the well and incubated for 48 h at 35 °C. Results showed that ginger essential oil exhibited significant antifungal activity against both groups of candida, but its potency was the lowest in comparison with cinnamon or oregano and thyme. They stated that the fluconazole-resistant group was more susceptible to this essential oil [41]. Moreover, a further *in vitro* study evaluated different components of ginger; three gingerols (6- gingerol, 8- gingerol, 10, gingerol) and three shagaols (6- shagaols, 8-shagaols, 10-shagaols) against fluconazole-resistant *C. albicans*. They used DMSO 0.1% as the control group, and the concentration of extracts was 0–500μg/ml. Their outcome was in the following order: 6-gingerol, 8-gingerol, and 6-shogaol demonstrated antibiofilm activity at levels 10, 50, 100μg/ml, while 10-gingerol, 8-shogaol, and 10-shogaol showed no effect even at 100μg/ml. In reality, they concluded that the antibiofilm activity of the compound was attributed to the number of carbon side chains, as carbon side chain numbers become weighty, antibiofilm event appeared to decrease [42].

16.8 Berberine

Berberine is identified as a defense compound in plants and protects them against microorganisms [36]. Some pharmacological effects of berberine are recognized, such as antiarrhythmic, anti-inflammatory and anticancer properties [93]. Several studies assessed the pharmacology and clinical efficacy of berberine and have suggested its antimicrobial, antifungal, and antivirus effects [36]. In an *in vitro* study, the effects of berberine alone and in combination with fluconazole and miconazole were investigated. They used 1.95–250 mg/l for berberine, 0.125–4 mg/l for miconazole, and 0.5–16 mg/l for fluconazole and added to the plate of candida species and incubated for 24 h at 37 °C. Results revealed that berberine showed antifungal activity against candida species, but non-albicans strains were more vulnerable than *C. albicans*. Also, they stated that berberine plus miconazole or fluconazole showed a strong synergic effect against both forms of *C. albicans* (planktonic and biofilm) [36]. In another *in vitro* study, the potential effect of berberine alone and in combination with fluconazole were analyzed against fluconazole-resistant *C. albicans*. 0.125–64μg/ml of fluconazole and 1–32μg/ml of berberine were used, and outcomes demonstrated that berberine and fluconazole alone had a weak antifungal activity. In contrast, a combination of these substances produced a large and significant inhibition zone in *C. albicans* plates [37]. In another *in vitro* study, the sensitization of *C. albicans* to terbinafine by BBR and berberrubine were analyzed. They applied 100μg/ml of materials in the plates and incubated for 48 h at 35 °C. their result's revealed that berberine and berberrubine (it is analog) alone showed small or no antifungal activity, but the combination of 100μg berberine and 6μg terbinafine showed significant antifungal activity, even when compared with terbinafine alone. They stated that berberine, in conjunction with terbinafine, does not show any inhibition zone on the well [35]. In contrast, an *in vitro* study showed that BBR might enter *C. albicans* cell and act in both extracellular and intracellular sites. BBR treatment will decrease ergosterol, so it leads to the loss of membrane permeability and cause the cell death of *C. albicans* . They assessed 5, 10, 25, 50 and 100μg/ml of berberine and added to the well and compared them with PBS. They incubated at 37 °C for 15 and 60 min. They concluded that berberine accumulation at a dose of 50μg/ml is time-dependent and suggested that berberine may serve as an alternative treatment for candidiasis [38]. Furthermore, a further *in vitro* study demonstrated that after 24 h of treatment with berberine, mitochondrial dysfunction was observed in fluconazole-resistant *C. albicans* strains. They stated that BBR prompts the apoptotic mechanism in fungus, which are resistant to fluconazole. In their study, they examined 0.125–64μg/ml of concentration of berberine against *C. albicans*, and incubation time lasts for 24 h at 35 °C. They showed that berberine reduced the number of *C. albicans* in all level due to induction of instability in the cell membrane of fluconazole-resistant strains [39].

16.9 Conclusion and Future Perspective

This review has comprehensively assessed the effects of nutraceuticals and other diet ingredients on *C. albicans* in oral candidiasis based on pre-clinical and clinical trials. The results have shown that almost all of the nutraceuticals and specific diet ingredients discussed above such as garlic, green tea, propolis, curcumin, licorice root, cinnamon, resveratrol, ginger, and berberine are useful in the treatment of *C. albicans* in oral candidiasis (Fig. 16.1). These nutraceuticals are not expensive without any major side effects compared to other pharmacological agents. However, most of the evidence was based on the *in vitro* situation and animal studies, so it is strongly recommended to conduct more clinical trials to show the effectiveness of these phytochemicals on humans as well as the optimum dose and duration of treatment.

Conflict of Interests None

Funding None

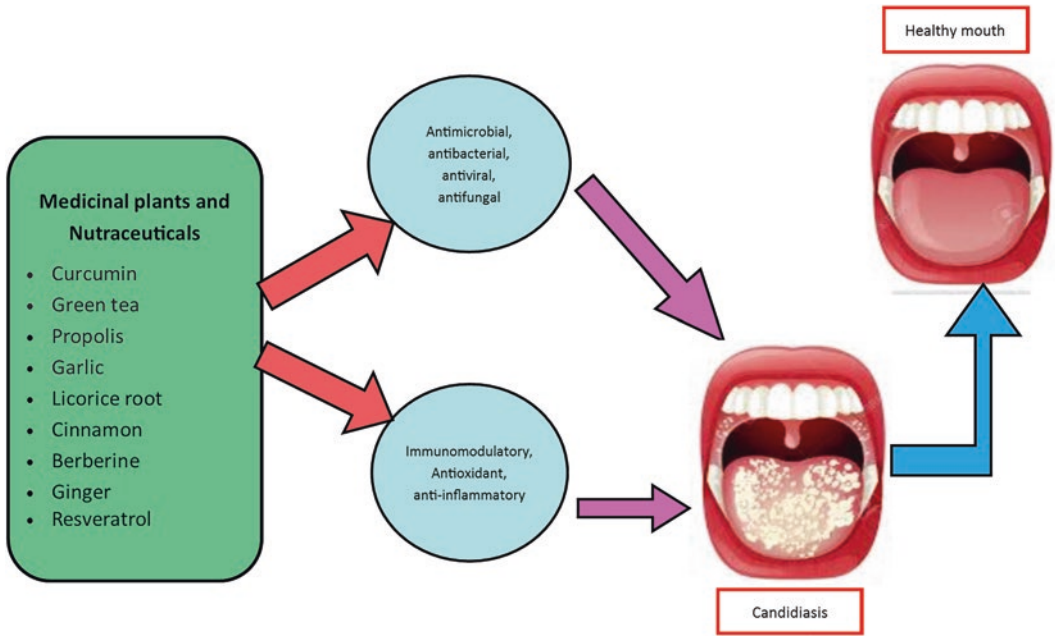

Fig 16.1 Schematic summary of the major mechanisms underlying the beneficial effects of nutraceuticals and herbal bioactive compounds on oral candidiasis

References

1. Rahayu RP, Prasetyo RA, Purwanto DA, Kresnoadi U, Iskandar RPD, Rubianto M (2018) The immunomodulatory effect of green tea (Camellia sinensis) leaves extract on immunocompromised Wistar rats infected by Candida albicans. Vet World 11(6):765–770
2. Varadarajan S, Narasimhan M, Malaisamy M, Duraipandian C (2015) Invitro anti-mycotic activity of hydro alcoholic extracts of some Indian medicinal plants against fluconazole resistant Candida albicans. J Clin Diagn Res 9(8):Zc07–Zc10
3. Rautemaa R, Ramage G (2011) Oral candidosis–clinical challenges of a biofilm disease. Crit Rev Microbiol 37(4):328–336
4. Capistrano HM, de Assis EM, Leal RM, Alvarez-Leite ME, Brener S, Bastos EM (2013) Brazilian green propolis compared to miconazole gel in the treatment of Candida-associated denture stomatitis. Evid Based Complement Alternat Med 2013:947980
5. Mendoza-Juache A, Aranda-Romo S, Bermeo-Escalona JR, Gomez-Hernandez A, Pozos-Guillen A, Sanchez-Vargas LO (2017) The essential oil of Allium sativum as an alternative agent against Candida isolated from dental prostheses. Rev Iberoam Micol 34(3):158–164
6. Pina GM, Lia EN, Berretta AA, Nascimento AP, Torres EC, Buszinski AF et al (2017) Efficacy of propolis on the denture stomatitis treatment in older adults: a multicentric randomized trial. Evid Based Complement Alternat Med 2017:8971746
7. Motsei ML, Lindsey KL, van Staden J, Jager AK (2003) Screening of traditionally used South African plants for antifungal activity against Candida albicans. J Ethnopharmacol 86(2–3):235–241
8. Bakhshi M, Taheri JB, Shabestari SB, Tanik A, Pahlevan R (2012) Comparison of therapeutic effect of aqueous extract of garlic and nystatin mouthwash in denture stomatitis. Gerodontology 29(2):e680–e684
9. Oliveira Jde A, da Silva IC, Trindade LA, Lima EO, Carlo HL, Cavalcanti AL et al (2014) Safety and tolerability of essential oil from Cinnamomum zeylanicum blume leaves with action on oral candidosis and its effect on the physical properties of the acrylic resin. Evid Based Complement Alternat Med 2014:325670
10. Thamburan S, Klaasen J, Mabusela WT, Cannon JF, Folk W, Johnson Q (2006) Tulbaghia alliacea phytotherapy: a potential anti-infective remedy for candidiasis. Phytother Res 20(10):844–850
11. Roque L, Duarte N, Bronze MR, Garcia C, Alopaeus J, Molpeceres J et al (2018) Development of a bioadhesive nanoformulation with Glycyrrhiza glabra L. extract against Candida albicans. Biofouling 34(8):880–892
12. Pavithra P, Janani V, Charumathi K, Indumathy R, Potala S, Verma RS (2010) Antibacterial activity of plants used in Indian herbal medicine. Int J Green Pharm (IJGP) 4(1):22

13. Erdogrul ÖT (2002) Antibacterial activities of some plant extracts used in folk medicine. Pharm Biol 40(4):269–273
14. Martin KW, Ernst E (2004) Herbal medicines for treatment of fungal infections: a systematic review of controlled clinical trials. Mycoses 47(3–4):87–92
15. Shahidi Bonjar G, Aghighi S, Karimi Nik A (2004) Antibacterial and antifungal survey in plants used in indigenous herbal-medicine of south east regions of Iran. J Biol Sci 4(3):405–412
16. Zorofchian Moghadamtousi S, Abdul Kadir H, Hassandarvish P, Tajik H, Abubakar S, Zandi K (2014) A review on antibacterial, antiviral, and antifungal activity of curcumin. Biomed Res Int 2014:186864
17. Behbehani JM, Irshad M, Shreaz S, Karched M (2019) Synergistic effects of tea polyphenol epigallocatechin 3-O-gallate and azole drugs against oral Candida isolates. J Mycol Med 29(2):158–167
18. Antunes DP, Salvia AC, de Araujo RM, Di Nicolo R, Koga Ito CY, de Araujo MA (2015) Effect of green tea extract and mouthwash without alcohol on Candida albicans biofilm on acrylic resin. Gerodontology 32(4):291–295
19. Ota C, Unterkircher C, Fantinato V, Shimizu MT (2001) Antifungal activity of propolis on different species of Candida. Mycoses 44(9–10):375–378
20. Freires IA, Queiroz V, Furletti VF, Ikegaki M, de Alencar SM, Duarte MCT et al (2016) Chemical composition and antifungal potential of Brazilian propolis against Candida spp. J Mycol Med 26(2):122–132
21. Martins RS, Pereira ES Jr, Lima SM, Senna MI, Mesquita RA, Santos VR (2002) Effect of commercial ethanol propolis extract on the in vitro growth of Candida albicans collected from HIV-seropositive and HIV-seronegative Brazilian patients with oral candidiasis. J Oral Sci 44(1):41–48
22. Gomaa OM, Gaweesh AS (2013) Variation in adhesion and germ tube formation of oral Candida using Egyptian propolis. Can J Microbiol 59(3):197–203
23. Fonseca-Santos B, Bonifacio BV, Baub TM, Gremiao MPD, Chorilli M (2019) In-situ gelling liquid crystal mucoadhesive vehicle for curcumin buccal administration and its potential application in the treatment of oral candidiasis. J Biomed Nanotechnol 15(6):1334–1344
24. Mahattanadul S, Mustafa MW, Kuadkaew S, Pattharachayakul S, Ungphaiboon S, Sawanyawisuth K (2018) Oral ulcer healing and anti-Candida efficacy of an alcohol-free chitosan-curcumin mouthwash. Eur Rev Med Pharmacol Sci 22(20):7020–7023
25. Daliri F, Azizi A, Goudarzi M, Lawaf S, Rahimi A (2019) In vitro comparison of the effect of photodynamic therapy with curcumin and methylene blue on Candida albicans colonies. Photodiagn Photodyn Ther 26:193–198
26. Seleem D, Benso B, Noguti J, Pardi V, Murata RM (2016) In vitro and in vivo antifungal activity of Lichochalcone-A against Candida albicans biofilms. PLoS One 11(6):e0157188
27. de Oliveira JR, de Castro VC, das Gracas Figueiredo Vilela P, Camargo SE, Carvalho CA, Jorge AO et al (2013) Cytotoxicity of Brazilian plant extracts against oral microorganisms of interest to dentistry. BMC Complement Altern Med 13:208
28. Irani M, Sarmadi M, Bernard F, Ebrahimi Pour GH, Shaker Bazarnov H (2010) Leaves antimicrobial activity of Glycyrrhiza glabra L. Iran J Pharm Res 9(4):425–428
29. Sharma H, Yunus GY, Agrawal R, Kalra M, Verma S, Bhattar S (2016) Antifungal efficacy of three medicinal plants Glycyrrhiza glabra, Ficus religiosa, and Plantago major against oral Candida albicans: a comparative analysis. Indian J Dent Res 27(4):433–436
30. Taguchi Y, Takizawa T, Ishibashi H, Sagawa T, Arai R, Inoue S et al (2010) Therapeutic effects on murine oral candidiasis by oral administration of cassia (Cinnamomum cassia) preparation. Nippon Ishinkin Gakkai Zasshi 51(1):13–21
31. Latti P, Ramanarayanan S, Prashant GM (2019) Antifungal efficacy of spice extracts against Candida albicans: an in vitro study. Indian J Community Med 44(Suppl 1):S77–s80
32. Veilleux MP, Grenier D (2019) Determination of the effects of cinnamon bark fractions on Candida albicans and oral epithelial cells. BMC Complement Altern Med 19(1):303
33. Almeida Lde F, Paula JF, Almeida RV, Williams DW, Hebling J, Cavalcanti YW (2016) Efficacy of citronella and cinnamon essential oils on Candida albicans biofilms. Acta Odontol Scand 74(5):393–398
34. Warnke PH, Becker ST, Podschun R, Sivananthan S, Springer IN, Russo PA et al (2009) The battle against multi-resistant strains: renaissance of antimicrobial essential oils as a promising force to fight hospital-acquired infections. J Craniomaxillofac Surg 37(7):392–397
35. Lam P, Kok SH, Lee KK, Lam KH, Hau DK, Wong WY et al (2016) Sensitization of Candida albicans to terbinafine by berberine and berberrubine. Biomed Rep 4(4):449–452
36. Wei GX, Xu X, Wu CD (2011) In vitro synergism between berberine and miconazole against planktonic and biofilm Candida cultures. Arch Oral Biol 56(6):565–572
37. Quan H, Cao YY, Xu Z, Zhao JX, Gao PH, Qin XF et al (2006) Potent in vitro synergism of fluconazole and berberine chloride against clinical isolates of Candida albicans resistant to fluconazole. Antimicrob Agents Chemother 50(3):1096–1099
38. Zoric N, Kosalec I, Tomic S, Bobnjaric I, Jug M, Vlainic T et al (2017) Membrane of Candida albicans as a target of berberine. BMC Complement Altern Med 17(1):268
39. da Silva AR, de Andrade Neto JB, da Silva CR, Campos Rde S, Costa Silva RA, Freitas DD et al (2016) Berberine antifungal activity in fluconazole-resistant pathogenic yeasts: action mechanism evaluated by flow cytometry and biofilm growth inhi-

bition in Candida spp. Antimicrob Agents Chemother 60(6):3551–3557
40. Aghazadeh M, Zahedi Bialvaei A, Aghazadeh M, Kabiri F, Saliani N, Yousefi M et al (2016) Survey of the antibiofilm and antimicrobial effects of Zingiber officinale (in vitro study). Jundishapur J Microbiol 9(2):e30167
41. Pozzatti P, Scheid LA, Spader TB, Atayde ML, Santurio JM, Alves SH (2008) In vitro activity of essential oils extracted from plants used as spices against fluconazole-resistant and fluconazole-susceptible Candida spp. Can J Microbiol 54(11):950–956
42. Lee JH, Kim YG, Choi P, Ham J, Park JG, Lee J (2018) Antibiofilm and antivirulence activities of 6-Gingerol and 6-Shogaol against Candida albicans due to hyphal inhibition. Front Cell Infect Microbiol 8:299
43. Okamoto-Shibayama K, Sato Y, Azuma T (2010) Resveratrol impaired the morphological transition of Candida albicans under various hyphae-inducing conditions. J Microbiol Biotechnol 20(5):942–945
44. Jung HJ, Seu YB, Lee DG (2007) Candicidal action of resveratrol isolated from grapes on human pathogenic yeast C. albicans. J Microbiol Biotechnol 17(8):1324–1329
45. Weber K, Schulz B, Ruhnke M (2011) Resveratrol and its antifungal activity against Candida species. Mycoses 54(1):30–33
46. Juin C, Perrin F, Puy T, Bernard C, Mollichella ML, Girardot M et al (2019) Anti-biofilm activity of a semi-synthetic molecule obtained from resveratrol against Candida albicans biofilm. Med Mycol 58:530
47. Sabitha P, Adhikari PM, Shenoy SM, Kamath A, John R, Prabhu MV et al (2005) Efficacy of garlic paste in oral candidiasis. Trop Dr 35(2):99–100
48. Ghorbani A, Sadrzadeh A, Habibi E, Dadgar K, Akbari J, Moosazadeh M et al (2018) Efficacy of Camellia sinensis extract against Candida species in patients with denture stomatitis. Curr Med Mycol 4(3):15–18
49. Santos VR, Gomes RT, de Mesquita RA, de Moura MD, Franca EC, de Aguiar EG et al (2008) Efficacy of Brazilian propolis gel for the management of denture stomatitis: a pilot study. Phytother Res 22(11):1544–1547
50. Santos VR, Pimenta FJ, Aguiar MC, do Carmo MA, Naves MD, Mesquita RA (2005) Oral candidiasis treatment with Brazilian ethanol propolis extract. Phytother Res 19(7):652–654
51. Mustafa MW, Ungphaiboon S, Phadoongsombut N, Pangsomboon K, Chelae S, Mahattanadul S (2019) Effectiveness of an alcohol-free chitosan-curcuminoid mouthwash compared with chlorhexidine mouthwash in denture stomatitis treatment: a randomized trial. J Altern Complement Med 25(5):552–558
52. Dovigo LN, Carmello JC, de Souza Costa CA, Vergani CE, Brunetti IL, Bagnato VS et al (2013) Curcumin-mediated photodynamic inactivation of Candida albicans in a murine model of oral candidiasis. Med Mycol 51(3):243–251
53. Sakima VT, Barbugli PA, Cerri PS, Chorilli M, Carmello JC, Pavarina AC et al (2018) Antimicrobial photodynamic therapy mediated by curcumin-loaded polymeric nanoparticles in a murine model of oral candidiasis. Molecules 23(8):2075
54. Karaman M, Arikan Ayyildiz Z, Firinci F, Kiray M, Bagriyanik A, Yilmaz O et al (2011) Effects of curcumin on lung histopathology and fungal burden in a mouse model of chronic asthma and oropharyngeal candidiasis. Arch Med Res 42(2):79–87
55. Casaroto AR, Lara VS (2010) Phytomedicines for Candida-associated denture stomatitis. Fitoterapia 81(5):323–328
56. Santezi C, Reina BD, Dovigo LN (2018) Curcumin-mediated photodynamic therapy for the treatment of oral infections-a review. Photodiagn Photodyn Ther 21:409–415
57. Sidhu P, Shankargouda S, Rath A, Hesarghatta Ramamurthy P, Fernandes B, Kumar Singh A (2018) Therapeutic benefits of liquorice in dentistry. J Ayurveda Integr Med 11:82
58. Borek C (2001) Antioxidant health effects of aged garlic extract. J Nutr 131(3):1010S–1015S
59. Tsai C-W, Chen H-W, Sheen L-Y, Lii C-K (2012) Garlic: health benefits and actions. Biomedicine 2(1):17–29
60. Kim J-a, Formoso G, Li Y, Potenza MA, Marasciulo FL, Montagnani M et al (2007) Epigallocatechin gallate, a green tea polyphenol, mediates NO-dependent vasodilation using signaling pathways in vascular endothelium requiring reactive oxygen species and Fyn. J Biol Chem 282(18):13736–13745
61. Murase T, Haramizu S, Shimotoyodome A, Tokimitsu I, Hase T (2006) Green tea extract improves running endurance in mice by stimulating lipid utilization during exercise. Am J Phys Regul Integr Comp Phys 290(6):R1550–R1556
62. Koo SI, Noh SK (2007) Green tea as inhibitor of the intestinal absorption of lipids: potential mechanism for its lipid-lowering effect. J Nutr Biochem 18(3):179–183
63. Ueda M, Nishiumi S, Nagayasu H, Fukuda I, Yoshida K-i, Ashida H (2008) Epigallocatechin gallate promotes GLUT4 translocation in skeletal muscle. Biochem Biophys Res Commun 377(1):286–290
64. Wolfram S (2007) Effects of green tea and EGCG on cardiovascular and metabolic health. J Am Coll Nutr 26(4):373S–388S
65. Sakata R, Nakamura T, Torimura T, Ueno T, Sata M (2013) Green tea with high-density catechins improves liver function and fat infiltration in non-alcoholic fatty liver disease (NAFLD) patients: a double-blind placebo-controlled study. Int J Mol Med 32(5):989–994
66. Khan N, Mukhtar H (2008) Multitargeted therapy of cancer by green tea polyphenols. Cancer Lett 269(2):269–280
67. Hakim IA, Harris RB, Brown S, Chow HS, Wiseman S, Agarwal S et al (2003) Effect of increased tea consumption on oxidative DNA damage among

smokers: a randomized controlled study. J Nutr 133(10):3303S–3309S
68. Stangl V, Lorenz M, Stangl K (2006) The role of tea and tea flavonoids in cardiovascular health. Mol Nutr Food Res 50(2):218–228
69. Bagherniya M, Nobili V, Blesso CN, Sahebkar A (2018) Medicinal plants and bioactive natural compounds in the treatment of non-alcoholic fatty liver disease: a clinical review. Pharmacol Res 130:213–240
70. Camargo LE, Pedroso LS, Vendrame SC, Mainardes RM, Khalil NM (2016) Antioxidant and antifungal activities of Camellia sinensis (L.) Kuntze leaves obtained by different forms of production. Braz J Biol 76(2):428–434
71. Aladag H, Ercisli S, Yesil DZ, Gormez A, Yesil M (2009) Antifungal activity of green tea leaves (Camellia sinensis L.) sampled in different harvest time. Pharmacogn Mag 5(20):437
72. Tamura M, Saito H, Kikuchi K, Ishigami T, Toyama Y, Takami M et al (2011) Antimicrobial activity of gel-entrapped catechins toward oral microorganisms. Biol Pharm Bull 34(5):638–643
73. Sanghani NN, Shivaprasad B, Savita S (2014) Health from the hive: propolis as an adjuvant in the treatment of chronic periodontitis-a clinicomicrobiologic study. J Clin Diagn Res 8(9):ZC41
74. Armutcu F, Akyol S, Ustunsoy S, Turan FF (2015) Therapeutic potential of caffeic acid phenethyl ester and its anti-inflammatory and immunomodulatory effects. Exp Ther Med 9(5):1582–1588
75. Zhu W, Chen M, Shou Q, Li Y, Hu F (2011) Biological activities of Chinese propolis and Brazilian propolis on streptozotocin-induced type 1 diabetes mellitus in rats. Evid Based Complement Alternat Med 2011:1
76. Nolkemper S, Reichling J, Sensch KH, Schnitzler P (2010) Mechanism of herpes simplex virus type 2 suppression by propolis extracts. Phytomedicine 17(2):132–138
77. Coelho L, Bastos E, Resende CC, Sanches B, Moretzsohn L, Vieira W et al (2007) Brazilian green propolis on helicobacter pylori infection. A pilot clinical study. Helicobacter 12(5):572–574
78. Santos V, Pimenta F, Aguiar M, Do Carmo M, Naves M, Mesquita R (2005) Oral candidiasis treatment with Brazilian ethanol propolis extract. Phytother Res: Int J Devoted Pharmacol Toxicol Eval Nat Prod Derivatives 19(7):652–654
79. Soleimani V, Sahebkar A, Hosseinzadeh H (2018) Turmeric (Curcuma longa) and its major constituent (curcumin) as nontoxic and safe substances: Review. Phytother Res 32(6):985-995.
80. Momtazi AA, Derosa G, Maffioli P, Banach M, Sahebkar A (2016) Role of microRNAs in the therapeutic effects of curcumin in non-cancer diseases. Mol Diagn Ther 20(4):335–345
81. Iranshahi M, Sahebkar A, Takasaki M, Konoshima T, Tokuda H (2009) Cancer chemopreventive activity of the prenylated coumarin, umbelliprenin, in vivo. Eur J Cancer Prev 18(5):412–415
82. Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A (2018) Curcumin as a potential candidate for treating hyperlipidemia: A review of cellular and metabolic mechanisms. J Cell Physiol 233(1):141–152.
83. Teymouri M, Pirro M, Johnston TP, Sahebkar A (2017) Curcumin as a multifaceted compound against human papilloma virus infection and cervical cancers: a review of chemistry, cellular, molecular, and preclinical features. Biofactors 43(3):331–346
84. Abrahams S, Haylett WL, Johnson G, Carr JA, Bardien S (2019) Antioxidant effects of curcumin in models of neurodegeneration, aging, oxidative and nitrosative stress: a review. Neuroscience 406:1–21
85. Bashang H, Tamma S (2020) The use of curcumin as an effective adjuvant to cancer therapy: a short review. Biotechnol Appl Biochem 67(2):171–179
86. Chandan S, Mohan BP, Chandan OC, Ahmad R, Challa A, Tummala H et al (2020) Curcumin use in ulcerative colitis: is it ready for prime time? A systematic review and meta-analysis of clinical trials. Ann Gastroenterol 33(1):53–58
87. Oglah MK, Mustafa YF, Bashir MK, Jasim MH (2020) Curcumin and its derivatives: a review of their biological activities. Syst Rev Pharm 11(3):472–481
88. Mollazadeh H, Cicero AFG, Blesso CN, Pirro M, Majeed M, Sahebkar A (2019) Immune modulation by curcumin: the role of interleukin-10. Crit Rev Food Sci Nutr 59(1):89–101
89. Lee JY, Lee JH, Park JH, Kim SY, Choi JY, Lee SH et al (2009) Liquiritigenin, a licorice flavonoid, helps mice resist disseminated candidiasis due to Candida albicans by Th1 immune response, whereas liquiritin, its glycoside form, does not. Int Immunopharmacol 9(5):632–638
90. Messier C, Grenier D (2011) Effect of licorice compounds licochalcone A, glabridin and glycyrrhizic acid on growth and virulence properties of Candida albicans. Mycoses 54(6):e801–e806
91. Utsunomiya T, Kobayashi M, Ito M, Pollard RB, Suzuki F (2000) Glycyrrhizin improves the resistance of MAIDS mice to opportunistic infection of Candida albicans through the modulation of MAIDS-associated type 2 T cell responses. Clin Immunol 95(2):145–155
92. Fatima A, Gupta VK, Luqman S, Negi AS, Kumar JK, Shanker K et al (2009) Antifungal activity of Glycyrrhiza glabra extracts and its active constituent glabridin. Phytother Res 23(8):1190–1193
93. Iwazaki RS, Endo EH, Ueda-Nakamura T, Nakamura CV, Garcia LB, Filho BP (2010) In vitro antifungal activity of the berberine and its synergism with fluconazole. Antonie Van Leeuwenhoek 97(2):201–205