Ashdin Publishing
Journal of Drug and Alcohol Research
Vol. 12 (2023), Article ID 236268, 8 pages
DOI: 10.4303/JDAR/236268

Review Article

Bioprospecting Yeast *Malassezia furfur*: A Source of Azelaic Acid

Dhanabalan Rangasamy* **and Stephy Rose Sebastian**

Department of Microbiology, RVS College of Arts and Science, India

**Address Correspondence to Dhanabalan Rangasamy, E-mail: dhanabalan@rvsgroup.com*

Received: 01 November 2023; Manuscript No: JDAR-23-120068; **Editor assigned:** 03 November 2023; PreQC No: JDAR-23-120068 (PQ); **Reviewed:** 17 November 2023; QC No: JDAR-23-120068; **Revised:** 22 November 2023; Manuscript No: JDAR-23-120068 (R); **Published:** 29 November 2023; **DOI:** 10.4303/JDAR/236268

Abstract

Fungi plays vital role in household, pharmaceutical and industrial processes. Among fungi several species of yeast are gaining importance in several industrial applications such as baking and alcoholic beverages. The yeasts are considered as a part in global food material by participating in different production processes. A unicellular, residential, opportunistic and lipophilic yeast *Malassezia furfur* has gained importance for its diverse range of metabolites including lactones, pityriarubins, melanin and flurochromes. In addition, the yeast develops ability to produce azelaic acid, a category of dicarboxylic acid in on the human skin. The C9 category Azelaic acid is known for its anti-inflammatory, anti-microbial, anti-keratinizing and recently antiparasitic activity. The human skin favours a suitable growth ground for the M. fufur to produce azelaic acid *in vivo* utilizing sebum lipids. The parameters suitable for optimal growth of *M. furfur* reflect in the azelaic acid production when suitable lipid sources are available. The present review describes actual secondary metabolites produced by the *M. furfur* and its role in various industrial sectors including cosmetics. Besides, the review gives a scope for the production of Azelaic acid by *M. furfur* in vivo, which will be a novel approach in the present scenario for the researchers.

Keywords: Azelaic acid; Yeast metabolites; Anti-parasitic activity; Anti-microbial activity

Introduction

The yeast species constitute an enormous and heterogeneous group of micro-organisms currently fascinating great attention among scientists for medical and industrial applications. Numerous and diverse biological activities confer yeasts as promising candidates in the food sectors, industrial and medical applications. The vital role of yeasts flavouring the fermented products, antagonistic toward undesirable bacteria, and fungi are now extensively known. The competitiveness of yeast for growth needs, its ability to withstand high ethanol concentrations, the acidity of the growth media, and its production of antimicrobial metabolites including antifungal assassin toxins or "mycocins" are all linked to its activities. Despite the fact the foods containing health beneficial probiotics by *Lactobacillus* and *Bifidobacterium*, and *Saccharomyces cerevisiae* var. *boulardii* has long been known effective for treating gastroenteritis.

Malassezia furfur, often referred to as Pityrosporum ovale, is a monophyletic genus of fungus that is typically found on the skin of humans and animals. It is one of the yeast species that is renowned for its medicinal significance. On human skin, commensals are commonly separated from both healthy and sick hosts. Its identification is related to a number of dermatological conditions, such as *Malassezia* folliculitis, Pityriasis Versicolor (PV), and Seborrheic Dermatitis (SD). However, it has also been taken into consideration for producing the organic saturated C9 dicarboxylic acid secondary metabolite Azelaic acid (AzA) on the skin. Industrially the AzA is produced by the ozonolysis of oleic acid, whereas naturally by *M. furfur*. Production of dicarboxylic acids such as malonic, succinic, glutaric, adepic, pimelic, suberic and sebacic acids are well documented, whereas the production of Azelaic Acid (AzA) from yeast *M. furfur* has not yet been documented. With the above elementary information the present review intends to outline *M. furfur*, Azelaic acid as well as its application.

Review of Literature

Microbial metabolites

In the present scenario microorganisms are considered as the propitious source for enormous number of natural products efficiently utilized in human, plant and veterinary life. Natural compounds from microorganisms are of great importance in nutrition, agriculture and healthcare. Primary metabolites, such as enzymes, amino acids, organic acids, vitamins, and alcohol are appropriately used as nutritional supplements and in the production of industrial commodities. On the other hand, apart from the plants or tissues the secondary metabolites are obtained from

the microbial population like bacteria, and yeast or fungi and their application in the biopharmaceutical industry are vast. Additionally, microorganisms and their products inevitably play a significant role in sustainable agriculture development [1].

The products of modern yeast biotechnology form the backbone of many commercially important sectors, including foods, beverages, pharmaceuticals, industrial enzymes and others. Saccharomyces cerevisiae, which according to EFSA (The European Food Safety Authority) has a QPS (Qualified Presumption of Safety) status, is the most common yeast used in food fermentation, where it has shown various technological properties. Yeasts do also play a significant role in the spontaneous fermentation of many indigenous food products [2]. A review on *S. cerevisiae* in African fermented foods has been provided by Jespersen. Several beneficial effects on human health and well-being have been reported and there seems to be a need to understand the positive effects of yeasts, their mechanisms and employment of them.

The major beneficial effects of yeasts, i.e., probiotic effects, biodegradation of phytate, folate bio-fortification and detoxification of mycotoxins have been summarized in a review [3]. However, there are other reported effects such as enrichment of foods with prebiotics as fructooligosaccharides, lowering of serum cholesterol, anti-oxidative properties, anti-mutagenic and antitumor activities [4-7]. Additional information on health significance and food safety of yeasts in foods and beverages has been focused by Fleet and Balia, 2006.

Yeast and their adaptations

Yeast species are unicellular eukaryotic fungi vividly grouped into the fungal kingdom based on the possession of a chitinous well-defined cell wall and devoid of peptidoglycan with lipid-linked ester. Morphologically vary from round to ovoid upto 10 µm in diameter exhibiting both asexual and asexual modes of reproduction [8]. Many types of yeast are isolated from sugar-rich environments, skins of fruits, fermented foods, exudates of plants, and resident in humans toe as skin flora, gut flora of mammals, insects and deep sea environment [9]. However the ecological biodiversity and function of yeasts are quite unknown compared to other micro-organisms [10,11]. Documented reports state their survival in both aerobic and anaerobic environments as well as biochemically as non-lactose and cellobiose fermenters. The ability of yeast survival temperature ranging from 5°C–35°C and freezing with decreasing viability has been reported [12]. Almost all yeast either exist in free state or constitute synergy such as parasitism, symbiosis, mutualism and competition with other micro-organisms [13]. Nutritionally their complete growth requirement is simple comprising carbon, nitrogen (ammonium salt, nitrate, amino acid, peptide, urea, purine and pyrimidine), phosphate, sulphate, trace amount of potassium, magnesium, calcium, iron, zinc and a vitamin source such as biotin, thiamine, pantothenic acid [14].

Yeast metabolites

Many yeast species secrete diverse inhibitory metabolites such as diacetyl, organic acids, mycocins, antibiotic factors, volatile acids, carboxylic acids and various other products capable of eliciting inhibition against food-borne pathogens and food spoilage micro-organisms, but the mechanism of inhibition is unknown [15,16]. Druvefors et al. (2005) stated that food fermentations naturally occurs by an interacting complex microbial population such as bacteria, mould and yeast. Reports on the synthesis of antimicrobial metabolites by yeasts are well documented, and such special features accord their suitability as biopreservative agent and starter cultures in food fermentation [17]. Similarly, Hara et al. (1980), Pfeiffer and Radler et al. (1984), Seki et al. (1985), Boone et al. (1990), Van Vuuren and Jacobs et al. (1992), Comitini et al. (2004) reported that genetically amended antagonistic yeast when inoculated into the fermenting medium as starter cultures contribute to enhanced security of food, sensory qualities and shelf life of the finished product by inhibiting the growth of associated pathogenic bacteria [18-24]. Young et al. (1987) and Boone et al. (1990), stated that starter culture of yeasts hinders the wild and undesirable yeast strains in the production of beer and bread as well as in food preservation and as a therapeutic agent [25-28]. Research findings observed that most of the yeast applications are based on exploiting its antagonistic capabilities, used in food and agriculture industries for the producing of microbiologically stable fermented food products with good organoleptic properties, bio-control agents for soil treatment and prevention of pre and post-harvest diseases of crops [29,30].

Yeast species like *Candida oleophila* has been registered as a standard bio-control agent for post-harvest crop diseases [31,32]. There is an increasing interest on yeast strains acting as antagonists toward spoilage or pathogenic microbes causing Gastrointestinal Tract (GIT) disorders and [33-35]. Many probiotic yeasts are inhibitory against pathogenic bacteria, Kumura et al. (2014), Psani and Kotzekidou et al. (2006), Klingberg et al. (2005), Generoso et al. (2010) had reported yeast species in probiotic preparations, and some reports confirmed the encouraging interaction of yeast with probiotic bacteria by augmenting their survival and stimulating their growth [36-42]. Kelsesidis and Pothoulakis et al. (2012) reported the yeast metabolites in treatment of diarrhoea and candidiasis [43]. Besides, Kurtzman et al. (2011) reported the efficiency of yeast single cell protein in quickening growth and conferring health benefits to in cattle feed when fed into them [44].

Yeast with antimicrobial properties

Certain types of yeasts may manufacture antimicrobials that block pathogenic and spoilage bacteria, making them unique agents for managing illness conditions and food deterioration. A few species of Candida, including *C. lusitaniae*, *C. tropicalis*, *C. kefyr*, and *C. intermedia*, have been shown to be able to control both gram positive and gram negative bacterial strains *in vitro*. The generation of volatile thermolabile toxic extract, antilisterial hydrophobic

peptides, and mycocins against bacterial infections may be responsible for yeast's antimicrobial effectiveness [45-47].

Malassezia furfur and its importance

The genus *Malassezia* has been a topic of intense basic research on taxonomy, physiology, biochemistry, ecology, immunology, and metabolomics. Currently, the genus encompasses 14 species *M. furfur*, *M. pachydermatis*, *M. sympodialis*, *M. globosa*, *M. obtusa*, *M. restricta*, *M. slooffia*, *M. dermatis*, *M. japonica*, *M. yamatoensis*, *M. nana*, *M. caprae*, *M. equina*, and *M. cuniculi*. Among all other *Malassezia* species *M.furfur* gains importance in causing common dermatologic disorders including Seborrheic Dermatitis (SD), Pityriasis Versicolor (PV), *Malassezia* folliculitis, Atopic Dermatitis (AD) and Psoriasis. The *Malassezia furfur* (formerly known as Pityrosporum ovale in its hyphal form) is a lipophilic yeast (a type of fungus) that is naturally found on the skin surfaces of humans and other mammals. Apart from its pathogenic characteristics the yeast is known for its wide range production of several indole alkaloids, e.g., pityriacitrin, malasseziaindole, pityriaanhydride and pityriarubin with proven biological activity [48]. Several biological properties such as UV protection, inhibition of oxidative burst in granulocytes, induction of apoptosis in human melanocytes, or tyrosinase inhibition have been described as putative biological functions for pigments of *M. furfur* [49]. Biochemical investigations showed that azelaic acid produced by *Malassezia spp*. is repressive to neutrophils and is a competitive inhibitor of tyrosinase, a key enzyme in melanogenesis, suggesting that azelaic acid may play an important role in abnormal skin pigmentation associated with PV [50,51].

Azelaic Acid: Properties and Mode of Action

Anti-inflammatory action of AzA

Reactive inflammation is a key pathogenic factor in acne caused by Propionibacterium acnes. The anti-inflammatory properties of AzA are well documented. Early research showed that topical application of a 20% AzA cream significantly reduced the number of lesions in patients with acne-in long-term treatment as well [52]. These data are in accordance with numerous clinical studies of acne. In 2 multi-center, randomized, controlled clinical trials recently conducted, topical application of AzA significantly reduced the numbers of inflammatory papules and pustules in subjects with acne. A similar effect was also demonstrated in a 1-year observational study [53]. The molecular mechanisms of the anti-inflammatory effect of AzA were examined in a trial using normal human keratinocytes was explained and the results showed that AzA suppressed UVB-induced interleukins IL-1β and IL-6, as well as TNF-α messenger Ribonucleic Acid (mRNA) expression and protein secretion [54]. The pro-inflammatory effect of UVB involves phosphorylation of the mitogen and stress-activated protein kinase p38 and the translocation of the redox-sensitive transcription factor κB p65 subunit (NF-κB p65) to the nucleus, where it activates the transcription of genes, including those for pro-inflammatory cytokine synthesis such as IL-1β, IL-6 or TNFα. AzA was found to significantly inhibit this process, and also induced the expression of peroxisome proliferator-activated receptor-γ, accompanied by inhibition of cell proliferation [55]. Another study showed that AzA promotes the down regulation of kallikrein 5 in epidermal keratinocytes, which in turn downregulates cathelicidins, decreasing inflammatory processes [56]. This process seems especially important for AzA's anti-inflammatory actions in rosacea [57]. In other experimental studies, the anti-inflammatory activity of AzA was attributed to its capacity to scavenge Reactive Oxygen Species (ROS) such as hydroxyl radicals (•OH) and superoxide anions ($\bullet O_2^-$) *in vitro*. AzA also reduced the release of superoxide and •OH released by neutrophils [51,58]. This evidence supports earlier studies that demonstrated the appreciable scavenging properties of AzA towards ROS produced in photoactivated chemical reactions [59-61].

Antibacterial action of AzA

The follicular microflora of acne lesions is dominated by *P. acnes*, *Staphylococcus epidermidis*, and *Malassezia furfur*. One approach is to treat patients either concomitantly or sequentially with a broad-spectrum antibacterial agent such as AzA. Unlike antibiotics, no resistant mutants are found after exposure to AzA, and it is also effective against antibiotic-resistant bacterial strains such as methicillin-resistant *Staphylococcus aureus*. Studies related to the topical 20% AzA cream inhibiting the growth of Staphylococci and Propionibacteria both *in vitro* and *in vivo* were reported, reducing both the surface bacteria and follicular bacteria populations. Another study demonstrated that the concentration of AzA in follicular casts exceeded the level required to inhibit the growth of *P. acnes* and *S. epidermis* (2 h-4 h after a single topical application) in all treated subjects [62,63]. AzA also acts against several other bacteria, including *S. aureus*, *Escherichia coli*, *Corynebacterium diphtheriae*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Leeming et al. 1986 reported that AzA has the same effects on these bacteria *in vitro* as it does on *P. acnes* and *S. epidermidis*.

Anti-keratinizing action of AzA

A report states that AzA is also an anti-keratinizing agent. Treatment with AzA leads to modification of epidermal keratinization, which particularly affects the terminal phases of epidermal differentiation, with a corresponding reduction in the size and number of keratohyalin granules and to no filament bundles. AzA also induces the swelling of the mitochondria and enlargement of the rough endoplasmic reticulum [64]. AzA treatment also reduces filaggrin expression in the stratum granulosum of patients with acne. Treatment with AzA also resulted in a reduced

thickness of the horny layer with a marked reduction in both number and size of keratohyalin granules [65]. The extent of the effect of AzA on the reduction of follicular hyperkeratosis is reported to be similar to that induced by retinoids.

In studies, AzA decreased keratinocyte DNA synthesis in a dose and time-dependent manner, and modulated differentiation of human epidermis as well as the synthesis of specific 95 kDa and 36 kDa proteins. These results show that AzA exerts reversible anti-proliferative effects on keratinocytes. AzA is a competitive inhibitor of important mitochondrial respiratory chain enzymes, such as reduced NADH dehydrogenase, succinic dehydrogenase and reduced ubiquinone cytochrome c oxidoreductase [66].

Influence of AzA on melanogenesis

In vitro studies show that AzA interferes with DNA synthesis and mitochondrial enzymes in abnormal melanocytes, but does not affect normal melanocytes. AzA can block tyrosinase activity by competitive inhibition [67-69]. AzA is also reported to have an inhibitory effect on DNA synthesis in melanoma cell [70]. This occurs when AzA is incorporated into the nuclei in a time-dependent manner and causes a dose-dependent inhibition of DNA synthesis. In addition, the inhibitory effect of AzA can be enhanced by the addition of zinc [71].

Azelaic acid with anti-parasitic activity

Azelaic acid (DB00548), an antibacterial medication, belongs to the family "Fatty acyls," which is projected to target 12 parasite metabolic proteins by aminoacylation [72]. The use of azelaic acid as a topical antibacterial agent is authorized and many metabolic enzymes in bacteria, including tyrosinase, respiratory chain mitochondrial enzymes, thioredoxin reductase, 5-α-reductase, and DNA polymerase, are thought to be inhibited by this medication. In fact, these groups of oxido-reductive enzymes include the 12 putative targets identified in *P. falciparum*, four of which are found in the apicoplast, a crucial organelle of the parasite. Given its capacity to specifically target several metabolic enzymes, azelaic acid presents itself as a promising repurposable option for treating *P. falciparum*. Such polypharmacological medications are capable of withstanding drug resistance in malarial parasites and are, in fact, quite valuable in terms of streamlining anti-malarial medication research and discovery activities. The information on the anticipated targets of azelaic acid is compiled in Table 1.

Pharmacokinetics of AzA in the skin

An *in vitro* study showed a 2.5-fold higher cutaneous penetration of AzA from a gel compared with a cream (8% vs. 3%, respectively). Percutaneous systemic absorption of AzA in humans is generally poor. Only about 3.6% of active substance applied is systemically absorbed. Data from a cutaneous penetration study that tested various moisturizing lotions showed that these may be applied either before or after 15% AzA gel without a major change in its cutaneous absorption profile [73].

***Malassezia furfur* in Azelaic acid production**

Malassezia furfur is lipophilic yeast grows in the presence of lipid sources. *Malassezia* species are dependent on exogenous lipids because they lack fatty acid synthase genes, except *M. pachydermatis* [74]. This explains their distribution on seborrheic skin areas (face, scalp and thorax), but they have been detected from most body sites except the feet [75]. References states that the yeast is capable of producing a category of Dicarboxylic acid called Azelaic acid. Biochemical investigations showed that azelaic acid produced by *Malassezia* spp. is repressive to neutrophils and is a competitive inhibitor of tyrosinase, a key enzyme in melanogenesis [51,76].

***Malassezia* metabolism and growth requirements**

All species in *Malassezia* genus, with the exception of *Malassezia* pachydermatis, are lipid dependent due to an inability to synthesize C14 or C16 fatty acids *de novo* and the dimorphism of the species has been recognized [77,78]. Many studies revealed the *Malassezia* growth sources and its adaptations publicized to induce the conversion of glycine, cholesterol and squalene, but not all species and strains able to undergo this phase transition [79]. The recognition of the *Malassezia* dimorphism was followed in 1986 by naming of the genus with all species and growth phases. All the species of *Malassezia* are biochemically and comparatively inert as they are very thick cell walled surrounded by a lamellar or 'capsular-like' layer made of lipids that can be removed with solvents [80].

Minimal medium with amino nitrogen and lipid source were found to be encouraging the growth of *M. furfur*, where the carbohydrates, vitamins, electrolytes and trace elements were not required. A study of nitrogen based auxanogram for *M. furfur* with 22 amino acids and 9 nitrogen sources revealed the growth of *M. furfur*, where all amino acids with the exception of cysteine were metabolized. It was also determined that ammonium salts, urea, creatine, creatinine, uric acid and allantoin. KNO_3, were failed to support the growth of *M. furfur*. The entire study exposed that based on the source used the yeast cells exhibited the change in the micromorphology as both oval and round forms. Assimilation of several amino acids specifically glycine and serine resulted in yeast dimorphism. Besides, the cell yield also differed depending on the nitrogen source, where the short-chain unbranched amino acids were utilized most readily. The yeast *M. furfur* is a relatively undemanding yeast species which can optimally adapt to the superficial skin environment, where all other lipid-dependent *Malassezia* species seem to require more complex media [48].

Recent report exposes one major feature of *Malassezia* yeasts is the requirement of lipids for growth, as most of their gene repertoire for carbohydrate metabolism has been lost. As the standard culture media in most clinics do not include lipid supplementation, the role of *Malassezia* in BSIs is likely underestimated [81].

Culture, identification and preservation of *Malassezia* species

The first successful culturing of *Malassezia* has been achieved by Panja, 1927 and acknowledged the external lipid source requirement for culturing. The Sabouraud's agar overlaid with sterile olive oil was found to good but the restriction is the enumeration of colonies or exhaustive examination as the colonies tend to coalesce. Besides the selective medias includes Dixon's medium, (containing Tween 40 and glycerol mono-oleate, and Leeming and Notman agar (containing Tween 60, glycerol and full fat cow's milk) [82,83].

For the re-classification of the *Malassezia* genus in 1996, sequencing of the large subunit rRNA and DNA/DNA reassociations were used. The biochemical methods of classification were were largely based on the micromorphology and the ability to use different Tweens as lipid sources that allowed better differentiation between similar species [84]. The major problem in working with *Malassezia* is the difficulty of preserving isolates, with certain species being particularly fastidious with lipid requirement. Few species such as *M. furfur*, M. sympodialis, and *M. pachydermatis* remain viable *in vitro* during storage. Other species like *M. obtusa*, *M. restricta* and *M. globosa* are difficult to maintain *in vitro* [85].

Discussion

Food security and safety have been impacted by the growing human population, making it necessary for research to look for other ways to support the adoption of more sustainable practices in order to fulfill the demands of people everywhere. Beneficial fungal metabolites are vital to the food, pharmaceutical, and cosmetics industries, as they have a substantial influence on human survival and health. The significance of fungal metabolites in human health and illness has been underlined in this review. Specialized metabolites are frequently the result of a sequence of cooperating biosynthetic enzymes that are present in the microorganisms. Azelaic acid, a naturally occurring C9 dicarboxylic acid present in wheat, rye, and barley, is one such metabolite.

Conclusion

This study begins with an overview of *Malassezia furfur*, kind of residential yeast commonly found on human skin, and its production of azelaic, a key metabolite. Furthermore, azelaic acid targets several metabolic enzymes in parasites and has demonstrated antiparasitic efficacy, offers a viable treatment alternative for disorders like malaria apart from its dermatological applications, antibacterial therapy, and possible repurposing in the treatment of other parasite illnesses.

Acknowledgement

None.

Conflict of Interest

The authors declare that they have no conflict of interest and the review has been made in the absence of any financial relationships.

References

1. R. Singh, M. Kumar, A. Mittal, P.K. Mehta, Microbial metabolites in nutrition, healthcare and agriculture, 3 Biotech, 7(2017):1-14.
2. EFSA's 2nd scientific colloquium report, European food safety authority, QPS, 2005.
3. S.M. Jenabian, L.L. Pedersen, L. Jespersen, Beneficial effects of probiotic and food borne yeasts on human health, Nutrients, 2(2010):449-473.
4. F. Maugeri, S. Hernalsteens, Screening of yeast strains for transfructosylating activity, J Mol Catal B Enzym, 49(2007):43-49.
5. E.I. Psomas, D.J. Fletouris, E. Litopoulou Tzanetaki, N. Tzanetakis, Assimilation of cholesterol by yeast strains isolated from infant feces and feta cheese, J Dairy Sci, 86(2003):3416-3422.
6. M. Klimek, S. Wang, A. Ogunkanmi, Safety and efficacy of red yeast rice (*Monascus purpureus*) as an alternative therapy for hyperlipidemia, 34(2009):313–327.
7. G. Kogan, M. Pajtinka, Babincova, E. Miadokova, P. Rauko, et al. Yeast cell wall polysaccharides as antioxidants and antimutagens: Can they fight cancer? Minireview, Neoplasma, 55(2008):387-393.
8. C.P. Kurtzman, N.P. Price, K.J. Ray, Production of sophorolipid biosurfactants by multiple species of the Starmerella (candida) bombicola yeast clade, FEMS Microbiol Lett, 311(2010):140-6.
9. E. Slavikova, R. Vadkertova, D. Vianova, Yeast colonizing leaf surface, J Basic Microbiol, 47(2007):344-350.
10. S.N. Kutty, T. Pape, A. Pont, B.M. Wiegmann, The muscoidea (diptera: Calyptratae) are paraphyletic: Evidence from four mitochondrial and four nuclear genes, Mol Phylogenet Evol, 49(2008):639-52.
11. E. Herrera, M.C. Sandoval, D.M. Camargo, T.F. Salvini, Motor and sensory nerve conduction are affected differently by ice pack, ice massage, and cold water immersion, Phys Ther, 90(2010):581-91.
12. H. Arthur, K. Watson, Thermal adaptation in yeast: Growth temperatures, membrane lipid, and cytochrome composition of psychrophilic, mesophilic, and thermophilic yeasts, J Bacteriol, 128(1976):56-68.
13. E. Goldman, Practical handbook of microbiology, 2nd ed, CRC Press, 2008.
14. T. Deak, Environmental factors influencing yeasts, Springer, 12(2006):155-174.
15. O.B. Oyewole, Lactic fermented foods in Africa and their benefits, Food Control 8(1997):289-297.

16. B. Viljoen, Yeast ecological interactions. Yeast' yeast, yeast' bacteria, yeast' fungi interactions and yeasts as biocontrol agents, In: Querol A, Fleet G (eds) Yeasts in food and beverages, Springer, 19(2006):83-110.

17. U.A. Druvefors, V. Passoth, J. Schurer, Nutrient effect on biocontrol of *Penicillium roqueforti* by *Pichia anomola* J121 during airtight storage of wheat, Appl Environ Microbiol, 71(2005):1865–1869.

18. S. Hara, Y. Iimura, K. Otsuka, Breeding of useful killer wine yeasts. Am J Enol Vitic, 31(1980):28–33.

19. P. Pfeiffer, F. Radler, Comparison of the killer toxin of several yeasts and the purification of a toxin of type K2, Arch Microbiol, 137(1984):357–361.

20. T. Seki, E.H. Choi, D. Ryu, Construction of killer wine yeast strain, Appl Environ Microbiol, 49(1985):1211–1215.

21. C. Boone, A. Sdicu, R. Degri, C. Sanchez, H. Bussey, Integration of the yeast "KI" killer toxin in gene into the genome of marked wine yeasts and its effect on vinification, Yeast, 41(1990):37–42.

22. H.J. Van Vuuren, C.J. Jacobs, Killer yeasts in the wine industry: A review, Am J Enol Vitic, 43(1992):119–128.

23. F. Comitini, I.J. De, L. Pepe, I. Mannazzu, M. Ciani, Pichia anomala and Kluyveromyces wickerhamii killer toxins as new tools against Dekkera/Brettanomyces spoilage yeasts, FEMS Microbiol Lett, 238(2004):235–240.

24. F. Comitini, N.D. Pietro, L. Zacchi, I. Mannazzu, M. Ciani, Kluyveromyces phaffii killer toxin active against wine spoilage: Purification and characterization, Microbiology, 150(2004):2535–2541.

25. T.W. Young, M. Yagiu, A comparison of the killer character in different yeasts and its classification, Genet Mol Biol, 44(1978):59–77.

26. C. Boone, A. Sdicu, R. Degri, C. Sanchez, H. Bussey, et al. Integration of the yeast "KI" killer toxin in gene into the genome of marked wine yeasts and its effect on vinification, Yeast, 41(1990):37–42.

27. V. Palpacelli, M. Ciani, G. Rosini, Activity of different "killer" yeasts on strains of yeast species undesirable in the food industry, FEMS Microbiol Lett, 68(1991):75–78.

28. J.C. Cailliez, N. Seguy, E.M. Aliouat, L. Polonelli, D. Camus, The yeast killer phenomenon, hypothetical way to control Pneumocytosis carinii pneumonia, Med Hypo, 43(1994):167-171.

29. S. Zhao, Y. Guo, Q. Wang, H. Luo, C. He, et al. Expression of flagellin at yeast surface increases biocontrol efficiency of yeast cells against postharvest disease of tomato caused by *Botrytis cinerea*, Postharvest Biol Technol, 162(2020):1-15.

30. I.S. Pretorius, Tailoring wine yeast for the new millennium+ovel approaches to the ancient art of winemaking, Yeast, 16(2000):675-729.

31. S.M. El-neshawy, C.L. Wilson, Nisin enhancement of biocontrol of postharvest diseases of apple with *Candida oleophila*, Biol Technol, 10(1997):9–14.

32. A. Santos, D. Marquinam, Killer toxin of Pichia membranifaciens and its possible use as a biocontrol agent against grey mould disease of grapevine, Microbiology 150(2004):2527-2534.

33. L. Sullivan, B. Murphy, P. McLoughlin, P. Duggan, P.G. Lawlor, et al. Prebiotics from marine macroalgae for human and animal health applications, Mar Drugs, 8(2010):2038-2064.

34. S. Maccaferri, A. Klinder, P. Brigidi, P. Cavina, A. Costabile, et al. Potential probiotic *Kluyveromyces marxianus* B0399 modulates the immune response in Caco-2 cells and peripheral blood mononuclear cells and impacts the human gut microbiota in an *in vitro* colonic model system, Appl Environ Microbiol, 78(2012):956-964.

35. A.J. Fernandez, J. Ata-Ali, T. Alegre-Domingo, E. Candel-Martí, F. Ata-Ali, The effect of orally administered probiotic *Lactobacillus* reuteri-containing tablets in peri-implant mucositis: A double-blind randomized controlled trial, J Periodontal Res 50(2015):775–785.

36. H. Kumura, Y. Tanoune, M. Tsukahara, T. Tanaka, K. Shimazki, Screening of dairy yeast strain and their potential probiotic application, J Dairy Sci, 87(2014):4050-4056.

37. M. Psani, P. Kotzekidou, Technological characteristics of yeast strains and their potential as starter adjuncts in Greek-style black olive fermentation, World J Microbiol Biotechnol, 22(2006):1329–1336.

38. T.D. Klingberg, L. Axelsson, K. Naterstad, D. Elsser, B.B. Budde, Identification of potential probiotic starter cultures for scandinavian-type fermented sausages, Int J Food Microbiol, 105(2005):419-431.

39. S.V. Generoso, M. Viana, R. Santos, F.S. Martins, J.A. Machado, et al. Saccharomyces cerevisiae strain UFMG 905 protects against bacterial translocation, preserves gut barrier integrity and stimulates the immune system in a murine intestinal obstruction model, Arch Microbiol, 192(2010):477–484.

40. V.J. Hodgson, D. Button, G.M. Walker, Anti-candida activity of a novel killer toxin from the yeast Williopsis mrakii, Microbiology, 141(1995):2003–2012.

41. Y. Katakura, R. Sano, T. Hashimoto, K. Ninomiya, S. Shioya, Lactic acid bacteria display on the cell surface cytosolic proteins that recognize yeast mannan, Appl Microbiol Biotechnol, 86(2010):319–326.

42. A.S. Suharaja, A. Henriksson, S.Q. Lin, Impact

of Saccharomyces cerevisiae on viability of probiotic *Lactobacillus* rhamnosus in termented milk under ambient conditions, J Food Process Preserv, 10(2012):1748–4549.

43. T. Kelsesidis, C. Pothoulakis, Efficacy and safety of the probiotic Saccharomyces *boulardii* for the prevention and therapy of gastro intestinal disorders, Ther Adv Gastroenterol, 5(2012):111–125.
44. C.P. Kurtzman, J.W. Fell, T. Boekhout, The yeasts: A taxonomic study, Elsevier.
45. B.C. Viljoen, Yeast ecological interactions, yeast'yeast, yeast'bacteria, yeast'fungi interactions and yeasts as biocontrol agents, In: Querol, A., Fleet, G. (eds) yeasts in food and beverages, Springer.
46. I.J. Hatoum, D.M. Greenawalt, C. Cotsapas, M.J. Daly, M.L. Reitman, et al. Weight loss after gastric bypass is associated with a variant at 15q26.1, Am J Hum Genet, 92(2013):827-34.
47. L. Chen, L. Jia, Q. Zhang, X. Zhou, Z. Liu, et al. A novel antimicrobial peptide against dental-caries-associated bacteria. Anaerobe, 47(2017):165–172. .
48. P. Mayser, U. Mrowietz, P. Arenberger, P. Bartak, J. Buchvald, et al. Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: Results of a double-blind, randomized, placebo-controlled, multicenter trial, J Am Acad Dermatol, 38(1998):539-47.
49. A.F. Kramer, S.J. Colcombe, E. McAuley, F. Scalf, K.I. Erickson, Fitness, aging and neurocognitive function, Neurobiol Aging, 1(2005):124-7.
50. A.S Breathnach, B. Martin, M. Nazzaro-Porro, S. Passi, G. Morpurgo, Effect of dicarboxylic acids on normal human melanocytes in culture, Br J Dermatol, 16(1978):19-20.
51. H. Akamatsu, J. Komura, Y. Asada, Inhibitory effect of azelaic acid on neutrophil functions: A possible cause for its efficacy in treating pathogenetically unrelated diseases. Arch Dermatol Res, 283(1991)162-166.
52. R.E. Mayer, Models for understanding, Rev Educ Res, 59(1989):43-64.
53. D. Thiboutot, B. Dréno, A. Layton, Acne counseling to improve adherence, Cutis, 81(2008):81-6.
54. A. Mastrofrancesco, M. Ottaviani, N. Aspite, G. Cardinali, E. Izzo, Azelaic acid modulates the inflammatory response in normal human keratinocytes through PPARgamma activation. Exp Dermatol, 19(2010):813-20.
55. S. Tyagi, P. Gupta, A.S. Saini, C. Kaushal, S. Sharma, The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. J Adv Pharm Technol Res, 2(2011):236-40
56. K. Yamasaki, K. Kanada, D.T. Macleod, A.W. Borkowski, S. Morizane, TLR2 expression is increased in rosacea and stimulates enhanced serine protease production by keratinocytes. J Invest Dermatol, 131(2011):688-97
57. B.E. Elewski, Z. Draelos, B. Dréno, T. Jansen, A. Layton, Rosacea-global diversity and optimized outcome: Proposed International consensus from the Rosacea International expert group. J Eur Acad Dermatol Venereol, 25(2011):188-200.
58. S. Passi, M. Picardo, C. De Luca, A.S. Breathnach, M. Nazzaro-Porro, Scavenging activity of azelaic acid on hydroxyl radicals *in vitro*, Free Rad Res Comm, 11(1991):329–339.
59. P.A. Grange, J. Raingeaud, V. Calvez, N. Dupin, Nicotinamide inhibits Propionibacterium acnes-induced IL-8 production in keratinocytes through the NF-kappaB and MAPK pathways, J Dermatol Sci, 56(2009):106-12.
60. M. Nazzaro Porro, S. Passi, M. Picardo, R. Mercantini, AS Breathnach Lipoxygenase activity of Pityrosporum *in vitro* and in vivo, J Invest Dermatol, 87(1986)108-112.
61. K. Yamasaki, R.L. Gallo, Rosacea as a disease of cathelicidins and skin innate immunity, J Investig Dermatol Symp Proc, 15(2011):12-15.
62. E.J. Van Hoogdalem, Transdermal absorption of topical anti-acne agents in man; review of clinical pharmacokinetic data, J Eur Acad Dermatol Venereol, 11(1998) 1:S13-19.
63. R.A. Bojar, A.G. Cutcliffe, K. Graupe, W.J. Cunliffe, Holland follicular concentrations of azelaic acid after a single topical application, Br J Dermatol, 129(1993):399-402.
64. A. Mayer-da-Silva, H. Gollnick, M. Detmar, J. Gassmüller, A. Parry, et al. Effects of azelaic acid on sebaceous gland, sebum excretion rate and keratinization pattern in human skin: An *in vivo* and *in vitro* study. Acta Derm Venereol Suppl (Stockh), 143(1989):20-30. [Google Scholar]
65. A. Farag, L. Ananieva, Acne vulgaris: Ultrastructure changes after treatment with 20% azelaic acid, J Dermatolog Treat, 6(1995):151-154.
66. B.C. Melnik, G. Schmitz, Role of insulin, insulin-like growth factor-1, hyperglycaemic food and milk consumption in the pathogenesis of acne vulgaris, Exp Dermatol, 18(2009):833-41.
67. L. Lemic-Stojcevic, A.H. Nias, A.S. Breathnach, Effect of azelaic acid on melanoma cells in culture, Exp Dermatol, 4(1995):79-81.
68. M. Nazzaro-Porro, S. Passi, L. Boniforti, F. Belsito, Effects of aging on fatty acids in skin surface lipids, J Invest Dermatol, 73(1979):112-7.
69. Q.H. Nguyen, T.P. Bui, Azelaic acid: Pharmacokinetic

and pharmacodynamic properties and its therapeutic role in hyperpigmentary disorders and acne, Int J Dermatol, 34(1995):75-84.

70. I. Galhaup, Azelaic acid: Mode of action at cellular and subcellular levels, Acta Derm Venereol Suppl (Stockh), 143(1989):75-82.
71. D. Stamatiadis, M.C. Bulteau-Portois, Mowszowicz, Inhibition of 5 alpha-reductase activity in human skin by zinc and azelaic acid, Br J Dermatol, 119(1988):627-32.
72. G. Ramakrishnan Chandra, N. Srinivasan, Exploring anti-malarial potential of FDA approved drugs: An *in silico* approach, Malar J, 290(2017):20-27.
73. J.Q. Del Rosso, The role of skin care as an integral component in the management of acne vulgaris: Part 1: The importance of cleanser and moisturizer ingredients, design, and product selection, J Clin Aesthet Dermatol, 6(2013):19-27.
74. M. Glatz, P.P. Bosshard, W. Hoetzenecker, P. Schmid Grendelmeier, The role of Malassezia spp. in atopic dermatitis, J Clin Med, 160(2015):20-27.
75. E.A. Grice, T.L. Dawson, Host-microbe interactions: Malassezia and human skin, Curr Opin Microbiol, Epub, 40(2017):81-87.
76. MNPS Passi, Effect of dicarboxylic acids in some pigmentary dermatoses, G Ital Dermatol, 113(1978):401-404.
77. S.E. Ahman, K.E. Bergström, Cutaneous carriage of Malassezia species in healthy and seborrhoeic Sphynx cats and a comparison to carriage in devon rex cats. J Feline Med Surg, 11(2009):970-6.
78. S. Alvarez-Perez, B. Lievens, T. Fukami, Yeast-bacterium interactions: The next frontier in nectar research, Trends Plant Sci, 24(2019):393-401.
79. H.R. Ashbee, R. Bond, Malassezia species and immunity: Host-pathogen interactions, Malassezia Skin, Springer, (2010):144–146.
80. E. Bensignor, D.N. Carlotti, Comparison of different cytological techniques for the detection of Malassezia pachydermatis on dog skin, Prat Med Chirurg animal Compag, 34(1999):33-41.
81. W. Rhimi, B. Theelen, T. Boekhout, D. Otranto, D. Cafarchia, Yeasts of emerging concern in fungemia, Front Cell Infect Microbiol. 10(2020):370.
82. N.J. Van Abbe, The investigation of dandruff, J Soc Cos Chem, 15(1964):609-630.
83. J.P. Leeming, F.H. Notman, Improved methods for isolation and enumeration of *Malassezia furfur* from human skin, J Clin Microbiol, 25(2017-2019).
84. J. Guillot, E. Gueho, M. Lesourd, Identification of Malassezia species, J Mycol Med, 6(1996):103-110.
85. E. Guého, G. Midgley, J. Guillot, The genus Malassezia with description of four new species Antonie van Leeuwenhoek, 69(1996):337-355.