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Biopharmaceuticals and Nutraceuticals Produced in Yeasts and the Clinical Management Related to COVID-19 Disease

Farzane Arianfar[1], Parastoo Tarighi[1], Marjan Shariatpanahi[2], Seyedeh Mona Mousavi Esfahani[1], Negar Mottaghi-Dastjerdi[3*]

1. Department of Medical Biotechnology, School of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran.
2. Department of Pharmacology and Toxicology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran.
3. Department of Pharmacognosy and Pharmaceutical Biotechnology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran.

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ABSTRACT

Recently, the market demand for biopharmaceuticals and nutraceuticals has increased. Consequently, high-volume production strategies have also drawn a lot of attention. The invention and development of recombinant DNA technology, using various hosts from bacteria to mammalian cells, have led to the industrial-scale manufacture of many valuable pharmaceutical products. Among the hosts, yeasts have a special place due to their numerous benefits. The present study deals with commercial yeast-derived biopharmaceuticals and laboratory-scale yeast-extracted nutraceuticals. It represents the biotechnological potential of yeasts to meet the market's needs in this area. Besides, considering the COVID-19 pandemic, the applications of yeast hosts for the clinical management of this disease have been briefly discussed.

*** Corresponding Author:**
Negar Mottaghi-Dastjerdi, PhD.
Address: *Department of Pharmacognosy and Pharmaceutical Biotechnology, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran.*
Phone: *+98 (21) 44606181*
E-mail: *mottaghi.n@iums.ac.ir*

Introduction

The development of biopharmaceuticals has been one of the world's largest and fastest-growing areas of the pharmaceutical industry in recent years, and its global market size is estimated to reach $400 billion by 2025 [1]. The development of recombinant DNA knowledge and its application in biotechnology has revolutionized the manufacturing of biopharmaceuticals [2]. Compared to conventional drugs, biopharmaceuticals possess many benefits, including specific targeting, fewer side effects [3], and higher specificity and activity [4]. Therefore, special notice has been established to produce biopharmaceuticals using various engineered hosts like mammalian cells, insects, *E. coli*, and yeast [5, 6]. However, each host has benefits and drawbacks (Figure 1).

In recent years, pharmaceutical commerce has taken a new approach to drug discovery, focusing on nutraceuticals [7]. The word "nutraceutical," as a mixture of nutrition and pharmaceutical, refers to food or portion that offers health profits and avoids and manages ailments [8]. Therefore, some pharmaceutical corporations were delighted to import nutraceuticals to the market due to their numerous pharmacological benefits for several diseases [9]. Their global market size reached nearly $230 billion in 2018 and is expected to be $336.1 billion by 2023 [10]. In this regard, "yeast extract"—the nutrient-rich cell material of yeasts—has been successfully applied to produce different types of nutraceuticals on a laboratory scale. The soluble parts of yeast cells make up yeast extract, a processed yeast product widely utilized in the food industry as a food flavoring, additive, vitamin supplement, and dietary source for bacterial growth media [11, 12]. A wealth of research [13, 14] has demonstrated the significance of employing yeast extract in industrial fermentation to produce microbial biomass or products. For the preparation of yeast extract, various yeast species, particularly *Saccharomyces cerevisiae*, have been used to make yeast extract or used as a nutritional supplement in bacterial growth media. Besides, their biological by-products serve as superb scaffolds in the manufacturing of nanoparticles. Moreover, they are efficient secretors of extracellular enzymes. Yeast cells can be grown and cultured in a fairly straightforward manner. Metal nanoparticles are produced through enzyme-mediated intracellular and extracellular reduction [15].

Another expression system, such as *E. coli*, has been recognized as a preferable host used to create recombinant proteins since it has a wide range of genetic tools, rapid growth, and straightforward methods for cultivating. However, using *E. coli* may be difficult or impossible based on the characteristics of the required protein. This situation is especially the case when the recombinant protein requires to undergo proteolytic processing, glycosylation, or other chemical modifications following translation. Consequently, the enzymes isolated from *E. coli* usually need to go via the experimental procedure to add posttranslational modifications. These additional steps to the protein synthesis process make the procedure even more expensive and re-

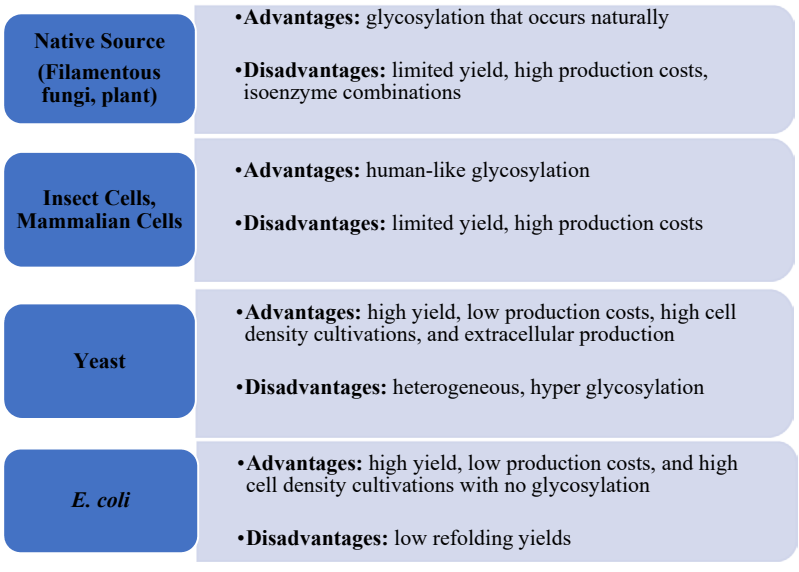

Figure 1. Advantages and disadvantages of expression hosts [107]

duce the quantity produced of the recombinant protein. As a result, eukaryotic hosts have been used as a substitute for in situ manipulation [16-20], to carry out most of the post-translational modifications necessary for a physiologically relevant recombinant protein. However, yeasts integrate the simple nature of a unicellular organism with fewer nutritional requirements than insect and mammalian cells. As a result, yeast bioassays for medical/health research have also been developed in several directions, especially for establishing large-scale screening approaches for novel medication research, mainly for mitochondrial malfunctions [21]. These bioassays go beyond the direct biosensing harmful chemicals. Yeast cells can be used for effective toxin transport analysis [22]. Considering the potential for drug development, some yeast-based bioassays have been developed to screen a variety of health risks to people. Below is a list of some instances.

Medications for malignancy

Human matrix metalloproteinases (MMPs) and the various dysfunctions they cause contribute to some serious disorders, particularly the emergence of tumors. Given their potential as therapeutic objectives, malignancy researchers seek antagonists of particular matrix metalloproteinases. A recombinant *Pichia pastoris* yeast strain was created by Diehl et al. that produce functional human MMPs at the cell surface, enabling the detection of MMPs [23]. The discovery of PI3K regulators is made possible by yet another screen based on the *S. cerevisiae* model [24].

Medications for anti-protozoans

Plasmodium parasites, particularly *P. falciparum*, which are spread to individuals by mosquito bites, is the cause of the potentially fatal disease malaria. Because of the emergence of immunity to earlier remedies, artemisinin is now the only effective medication to treat malaria. To search for new treatments and understand better the medication's mechanism of activity, a bioassay has been devised in *S. cerevisiae* to test for substances with artemisinin-like activity [25].

Medications against prions

Growing yeast has been demonstrated to be an effective tool for investigating prions [26, 27]. Bach et al. developed a medicine active against mammals employing the preservation of the biochemical routes controlling prions generation and retention between yeasts and mammals [28, 29]. Their strategy was confirmed as a successful rapid screening technique to find prion blockers. It enabled the identification of a novel family of chemicals, the kastellpaolitines, capable of accelerating mammalian prion clearance.

In this review, we studied the investigations published on the employment of yeast hosts for the industrial manufacture of FDA-approved pharmaceuticals and laboratory-scale production of nutraceuticals.

There are similar articles in this field, but they are still incomplete and outdated. The present study provides a comprehensive and up-to-date overview of this subject.

Yeast hosts

S. cerevisiae

S. cerevisiae was the primary yeast expression platform developed to produce recombinant therapeutic proteins. Using *S. cerevisiae* as a cell factory has a considerable benefits like the ability to secrete a biologically active form of eukaryotic proteins; its good adaption to difficult conditions in large-scale environments is particularly highlighted in the pharmaceutical industry. *S. cerevisiae* was employed as an efficient host organism to generate different commercial recombinant therapeutic proteins [8, 9, 30, 31]. Furthermore, *S. cerevisiae* was known to produce numerous nutraceuticals [32-36]. However, this host still has several drawbacks, including the production of alien glycoforms like hyperglycosylation, plasmid instability, and low protein yields [37]. Therefore, recent investigations have directed to expanding alternative yeast expression platforms to overcome the mentioned problems.

P. Pastoris

P. pastoris, as an alternative yeast expression system, has gained much consideration due to its highly efficient intracellular and extracellular secretory expression [38, 39]. As a host, *P. pastoris* exhibits several benefits, including powerful methanol-regulated promoters [40, 41], the possibility to reach high cell density cultures [42], capacity to perform various eukaryotic posttranslational modifications [43], hassle-free extraction of secreted proteins as a result of the low extent of in-house proteins in the extracellular environment [37], and assignment of GRAS (generally regarded as safe) description via Food and Drug Administration (FDA) [44]. Because of these advantages, *P. pastoris* is broadly consumed to produce several recombinant heterologous proteins [37, 45-47]. Despite many desirable features, *P. pastoris* has few drawbacks like high concentrations of proteases and hazards associated with large amounts of accumulated methanol [48].

Hansenula polymorpha (*Pichia angusta*)

Hansenula polymorpha (*Pichia angusta*), like *P. pastoris*, has a methanol-assimilating pathway; therefore, it can propagate on methanol as the self-sufficient carbon and energy source [37]. Compared to other methyl trophic yeast strains, *H. polymorpha* has a few unique features, including the capability of nitrate assimilation and heat tolerance up to 50°C [49]. *H. polymorpha* is one of the ideal alternative platforms to produce recombinant protein due to the strong inducible promoters belonging to the methanol utilization pathway [50], efficient secretion [51], high productivity value [52], less hyperglycosylation activity compared to *S. cerevisiae* [37], and outstanding storage capacity for heterologous membrane proteins [53] fused to an appropriate signal peptide [54]. Today, a few market-available recombinant therapeutics are produced using *H. polymorpha* [55]. However, despite the beneficial features of *H. polymorpha* to produce biopharmaceuticals, some challenges and limitations are present like the particular host strain and product as well as protein retention in the endoplasmic reticulum [56], damaged processing [55, 57], and proteolytic degradation [58].

Yarrowia lipolytica

Researchers extensively study *Y. lipolytic*a as a non-conventional yeast due to its notable features, including its inherent ability to secrete a broad range of products, GRAS status, low level of hyperglycosylation, and high level of product yield [59]. Therefore, several genetically engineered strains of this yeast are employed for the laboratory-scale manufacturing of several pharmacologically important products, such as biopharmaceuticals and nutraceuticals [60-64]. Despite its potential application, using *Y. lipolytica* still requires laborious procedures of strain expansion to reach the maximum yield and productivity [65].

There is no single yeast platform ideal for manufacturing all possible products. Consequently, a parallel assessment of potential yeast platforms is essential to find a suitable host for optimal targeted industrial purposes. This article describes yeast-derived biopharmaceuticals and nutraceuticals based on the host used for their biomanufacturing.

Table 1. Saccharomyces cerevisiae-derived biopharmaceuticals [64]

Category	Protein	Brand Name	Company	Therapeutic Application
Blood factors	Human albumin (HA)	Recombumin [108]	Albumedix	Stabilization of the biological drugs and vaccines formulation
	Factor XIII A-subunit	Tretten [109]	Novo Nordisk	Congenital factor XIII A-subunit deficiency
Tissue plasminogen activator	Lepirudin (recombinant hirudin)	Refludan	Bayer HealthCare	Anticoagulation treatment of heparin-induced thrombocytopenia
	Desirudin (recombinant hirudin)	Iprivask Revasc	Canyon Pharmaceuticals	Inhibition of venous thrombosis
Cytokines	Sargramostim (rhu GM-CSF)	Leukine	Bayer HealthCare	Cancer, bone marrow transplant
	Molgramostim (rGM-CSF)	Leucomax	Novartis	
Recombinant hormones	Insulin aspart Insulin detemir Insulin degludec	NovoLog Levemir Tresiba [110]	Novo Nordisk	Diabetes mellitus
	Somatropin (growth hormone)	Declage1 [111]	BioPartners	Short stature/Somatotropin deficiency
	Liraglutide (a glucagon-like peptide1 correspondent with linked fatty acid)	Victoza	Novo Nordisk	Type 2 diabetes
	Glucagon	GlucaGen	Novo Nordisk	Hypoglycemia
	Becaplermin (a recombinant human platelet-derived growth factor (rhPDGF-BB)	REGRANEX	Raritan	Lower extremity diabetic Neuropathic ulcers
		Augment Bone Graft [112] AUGMENT injectable (AI) [113]	BioMimetic Therapeutics, LLC	As an alternative to autograft in arthrodesis of the ankle and or hindfoot
		GEM 21STM [114]		Remedy for intrabony periodontal problems, furcating periodontal defects, gingival decline related to periodontal problems

Category	Protein	Brand Name	Company	Therapeutic Application
Recombinant vaccines	Hepatitis B surface antigen	Recombivax	Merck	Vaccination against Hepatitis B
		Comvax		Protection against H. influenza type B and Hepatitis B
		HBVaxPro	Sanofi Pasteur and Merck (MSD)	Immunization against Hepatitis B
		Hexavax	Sanofi	Protection against tetanus, diphtheria, pertussis, polio, Hemophilus influenza type B, and Hepatitis B
		Procomvax		Vaccination against infections instigated by all identified subtypes of the Hepatitis B virus
		Euvax B	LG Life Sciences Ltd	H. influenza type B and Hepatitis B
		Ambirix	GlaxoSmithKline	Prevention of Hepatitis A and B
		Pediarix		Protection against Hepatitis B
		Twinrix		Protection against Hepatitis A and B
		Tritanrix-HB		Immunization against diphtheria, pertussis, tetanus, and Hepatitis B
		Infanrix-hexa		Immunization against Haemophilus influenza type B, diphtheria, tetanus, pertussis, polio, and Hepatitis B
		Infanrix Hep B		Prevention of Hepatitis B, diphtheria, pertussis, and tetanus
		Infanrix-Penta		Prevention of diphtheria, pertussis tetanus, polio, and Hepatitis B
		Engerix-B		Immunization against Hepatitis B
		Fendrix		Vaccination against Hepatitis B
		Primavax	Pasteur merieux	Prevention of diphtheria, tetanus, Hepatitis B
	RTS, S (portion of *P. falciparum* circumsporozoite protein fused with Hepatitis B surface antigen [RTS], and combined with Hepatitis B surface antigen [S]), in the form of non-infectious viruslike particles2 [115]	Mosquirix [116]	GlaxoSmithKline	Protection against Hepatitis B in situations where malaria prevention is required
	Virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, and 18	Gardasil	Merck	Vaccination against ailments generated through the specified types of HPV included
	Virus-like particles (VLPs) of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58	Gardasil 9		Vaccination against diseases created by the specified types of HPV included in the vaccine
Recombinant enzymes	Rasburicase (a recombinant urate oxidase enzyme)	ELITEK	Sanofi	Hyperuricemia
	Albiglutide (a GLP-1 receptor agonist)	TANZEUM	GlaxoSmithKline	Type 2 diabetes

[1]This medicine is now withdrawn from use in the European Union

[2]The phase III trial for evaluating the efficacy and safety was carried out at 11 trial sections in seven African countries with various malaria transference severity and patterning. There is no WHO guideline suggestion for the bulky usage of the RTS, S malaria vaccine after the pilot schedule.

Table 2. Production of nutraceuticals in *S. cerevisiae*

Category	Protein	Therapeutic application
Phenylpropanoids	Naringenin (flavanone) [33]	Anti-hepatitis C virus [117], antiaging [118-120], anti-alzheimer [121], antiasthma [122], anticancer [123], antidiabetic [124-128], antimicrobial [129], antioxidant [130]
	Resveratrol [32, 34]	Antioxidant [131], anticancer [132, 133], cardioprotective [134, 135], neuroprotective [136, 137], Anti-inflammatory [137], Antimicrobial [138]
	Fisetin [30]	Antioxidant [139], anticancer [140], neuroprotective [141]
	Scutellarin [142]	Cardio- and cerebro-vascular diseases prevention [71]
	Anthocyanin (pelargonidin-3-O-glucoside, cyanidin-3-O-glucoside, delphinidin-3-O-glucoside) [143]	Antioxidant, neuroprotective, antidiabetic, anti-inflammatory, improvement of vision, cardioprotective [71]
	Dihydrochalcones (phlorizin, naringin dihydrochalcone, nothofagin) [144]	Antioxidant, hypoglycemic agent [71]
	Salidroside [145]	Anticancer, protection of the cardiovascular system, nerve cells, and brain [71]
Flavonoid derivatives	Genistein [146]	
	Kaempferol [30]	Anti-inflammatory [147], anticancer [148], cardioprotective [149], neuroprotective [150]
	Quercetin [30]	Anti-Inflammatory [151], anti-obesity [152], anticancer [153]
	Liquiritigenin [30]	Neuroprotective [68], anti-depression [154], improvement of learning and memory [155]
	Resokaempferol [30]	
Terpenoids	Lycopene [35]	Anticancer [156], antioxidant [157], antidiabetic [158], anti aging [159]
	Astaxanthin [36]	Antioxidant [160], anti-inflammatory [161], anti apoptotic [162], retinal diseases [163]
	Limonene [164]	Antibacterial and insecticide [71]
	Sabinene [164]	Antibacterial and insecticide [104]
	Geraniol [165]	Antimicrobial and antitumor [71]
	a-terpineol [166]	Anti-fungal [71]
	Artemisinic acid [167]	Antimalarial [71]
	Valerenic acid [168]	Anxiolytic and sedative [71]
	Patchoulol [169]	Neuroprotection, anti-inflammatory, and anticancer [71]
	Sclareol [170]	Antibacterial and fragrances [71]
	Miltiradiene [171]	Anticancer, antibacterial, and anti-inflammatory [71]
	Hydrocortisone [171]	Anti-inflammatory [71]
	Carnosic acid [172]	Antitumor, antioxidant, and anti-inflammatory [71]
	Ginsenoside Rh2 [173]	Prevention and treatment of cancer [71]
	Ginsenoside Rg3 [174]	Anticancer and anti-tumor [71]
	Glycyrrhetinic acid [175]	Antiviral, antiallergic, liver protection, and antiulcer [71]

Category	Protein	Therapeutic application
	Strictosidine [176]	Anti-cancer [71]
	Opioids (thebaine, hydrocodone) [73]	Analgesic [71]
Alkaloids	Noscapine [74]	Anticancer and antitussive [71]
	Tropine [103]	Treatment for the neurological disorder [71]
	Pseudotropine [177]	Anticholinergic [71]

Yeast-based products

S. cerevisiae-based products

Biopharmaceuticals

S. cerevisiae, as a first-choice yeast host cell, is used to produce 20% of biopharmaceuticals [66]. Therefore, several strains of this yeast consisting of wild-type and mutant ones are applied for protein expression [67]. BJ5464 is an *S. cerevisiae* dominant strain for recombinant protein production [68]. Numerous *S. cerevisiae*-derived biopharmaceuticals have been approved for human use, which can be categorized into different groups (Table 1).

Nutraceuticals

As a significant industrial host, *S. cerevisiae* can produce nutraceutical ingredients. Furthermore, it can be genetically manipulated to produce targeted substances in relatively high amounts [69]. Several examples of nutraceuticals produced in *S. cerevisiae* are provided in Table 2.

P. pastoris-based products

Biopharmaceuticals

P. pastoris expression platform is being efficaciously utilized to create several FDA-approved biopharmaceuticals which have already found their way to the market. Besides, there are several commercially-available recombinant proteins produced in *P. pastoris* for research purposes, like human stem cell factor, human serum albumin and interferon (HSA-IFN)-α 2b, murine tumor necrosis factor (TNF)-α, ovine interferon (IFN)-τ and recombinant human angiostatin [70]. *P. pastoris* expression strains are generally descendants of the NRRL-Y 11430 strain [39]. Novel strains such as GS115 and GS200 have emerged due to mutations in the auxotrophic genes and could grow in the least media enriched with histidine and arginine [44]. Table 3 presents several FDA-approved biopharmaceutical compounds manufactured in *Pichia* for human application.

Nutraceuticals

P. pastoris, as a methylotrophic yeast, has also been designed to manufacture some nutraceuticals (Table 4). However, the number of nutraceuticals produced in *P. pastoris* is much fewer than that in *S. cerevisiae* due to the limited genetic tools available for the metabolic engineering of this yeast [71].

Hansenula polymorpha-based products

Biopharmaceuticals

Several commercially-available biopharmaceuticals have been successfully produced in *H. polymorpha* due to developments in genome editing technology, transformation optimization, and cultivation strategies [72] (Table 5). The most frequently used *H. polymorpha* strains for producing recombinant proteins are the DL-1 (NRRL-Y-7560; ATCC26012), CBS4732 (CCY38-22-2; ATCC34438, NRRL-Y-5445), and NCYC495 (CBS1976; ATAA14754, NRLLY-1798).

Y. lipolytica-based products

Biopharmaceuticals

Y. lipolytica was considered a suitable host for the laboratory-scale production of several biopharmaceutical proteins (Table 6). According to various investigations, a 10–20 fold growth in the heterologous manufacture of these proteins can be achieved by consuming multicopy vectors [73, 74] and scaling-up strategies [132, 133]. The most employed host strains for making heterologous proteins in Yarrowia are E129 and the Po1 derivatives (Po1d, f, g, and h) [75].

Table 3. *P. pastoris*-derived biopharmaceuticals [178]

Category	Protein	Brand Name	Company	Therapeutic Application
Blood factors	Ecallantide (DX-88), a recombinant kallikrein inhibitor protein	Kalbitor	Dyax (Cambridge, MA)	Hereditary angioedema treatment
	Recombinant human serum albumin	Medway	Mitsubishi Tanabe Pharma (Japan)	Blood volume expansion
	Recombinant microplasmin (Ocriplasmin)	Jetrea	ThromboGenics (Belgium)	Vitreomacular adhesion (VMA) treatment
Recombinant hormones	Recombinant human insulin	Insugen Basalog [70]	Biocon (India)	Diabetes treatment
	Heparin-binding EGF-like growth factor	HB-EGF	Trillium (Canada)	Interstitial cystitis treatment/Treatment of bladder pain syndrome (IC/BPS)
Cytokines	Recombinant interferon-alpha 2b	Shanferon™	Shantha/Sanofi (India)	Treatment of cancer & Hepatitis C
Recombinant vaccines	Recombinant Hepatitis B vaccine	Shanvac ™	Shantha/Sanofi (India)	Prevention of Hepatitis B
Recombinant enzymes	Recombinant trypsin	-	Roche Applied Science (Germany)	Digestion of proteins
	Recombinant collagen	-	Fibrogen (San Francisco, CA)	Medical research reagents/ dermal filler
Nanobody	Recombinant anti-IL6 receptor single domain antibody fragment	Nanobody ALX-0061	Ablynx (Belgium)	Rheumatoid arthritis treatment
	Recombinant anti-RSV single domain antibody fragment	Nanobody ALX00171	Ablynx (Belgium)	Treatment of respiratory syncytial virus (RSV) infection

Nutraceuticals

Y. lipolytica, as a non-conventional oleaginous yeast, is broadly utilized to produce different nutraceuticals (Table 7).

Yeast-expressed products and COVID-19

The emergence and wide spread of coronavirus disease 2019 (COVID-19), produced by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has resulted in many deaths [76]. Therefore, after the recent pandemic outbreak of COVID-19, the scientific associations collaborated to find therapeutic and preventative clarifications [77]. In this regard, yeasts might play a critical role in numerous fields like vaccine production, genetic manipulation of the virus genome, and manufacturing of medicines.

Recombinant protein vaccines

Yeast is a promising platform for producing recombinant vaccines since it possesses several advantages, including rapid growth, easy genetic manipulation, extracellular secretion of recombinant proteins, and adding certain PTMs [78]. Recombinant protein subunit vaccines, also called recombinant subunit vaccines, are a distinguished group of vaccines composed of purified immunogenic proteins or peptides that are virus deriva-

Table 4. Production of nutraceuticals in *P. pastoris*

Category	Protein	Therapeutic Application
Phenylpropanoids	30-Hydroxygenistein [179]	Antioxidant, anti proliferative, Anti-inflammatory, and anti-melanogenesis [71]
Terpenoids	(+)-Nootkatone [180]	Anti-platelet aggregation and anti proliferative [71]
	(+)-Ambrein [181]	Anti-nociceptive and aphrodisiac [71, 181]
	Lycopene [182]	Anticancer [144], antioxidant [143], antidiabetic [145], anti aging [146]

Table 5. Hansenula polymorpha-derived biopharmaceuticals [183-185]

Category	Protein	Brand Name	Company	Therapeutic Application
Tissue plasminogen activator	Hirudin	Thrombexx	Rhein Minapharm[1]	Treatment of hematoma, thrombophlebitis, and shunt thrombosis prophylaxis
Recombinant hormones	An intermediate-acting and a short-acting type of insulin	Wosulin	Wockhardt	Type 2 diabetes mellitus
Cytokines	IFNa-2a	Reiferon	Rhein Minapharm	Hepatitis C
Recombinant vaccines	HBsAg	Hepavax-gene	Berna Biotech Korea Corporation, a Crucell Company	Immunization against Hepatitis B
		GeneVac-B	Serum Institute of India	
		Biovac-B	Wockhardt	
		AgB	Laboratorio Pablo	
		Heplisav B	Dynavax GmbH	

[1]This company has also launched extrauma as the first worldwide topical recombinant hirudin. This product is used as an anti-thrombotic and anti-inflammatory agent

tives [79]. Most of the investigations about SARS-CoV subunit vaccines have focused on the "S" protein and particularly its highly immunogenic receptor binding domain (RBD) [80, 81]; the results of these investigations underlined the potential benefits of SARS-CoV subunit vaccines against COVID-19 [82-87].

P. pastoris yeast is a suitable platform for the industrial manufacture of pharmaceuticals and vaccines (Table 3). One study reported antibody generation in mice following the RBD antigen of SARS-CoV-2 expressed in *P. pastoris*, indicating the capability of this yeast to produce an effective SARS-CoV subunit vaccine. Besides, RBD obtained from *P. pastoris* showed a similar structure and stability to that produced in HEK-293T cells [88]. There-

Table 6. Laboratory-scale production of biopharmaceuticals in *Y. lipolytica*

Category	Protein	Therapeutic Application
Tissue plasminogen activator	Tissue plasminogen activator [186]	Treatment of hematoma, thrombophlebitis, and shunt thrombosis prophylaxis
Recombinant hormones	Proinsulin analog (10 kDa) Insulinotropin (4 kDa) [187]	Diabetes treatment
	Epidermal growth factor (6 kDa) [188]	Wound healing [189]
Cytokines	Human interferon alpha 2b (hIFN α2b) [190, 191]	An antiviral and antineoplastic drug [192]
Pro-inflammatory polypeptides	Anaphylatoxin C5a [193]	Anti-inflammatory effects in ischemia/Reperfusion injury, allergic asthma, rheumatoid arthritis, and age-related macular degeneration [194]
Blood factors	Blood coagulation factor XIIIa (80 kDa) [195]	The main factor in blood coagulation [196]
Antibody	Anti-Ras single-chain antibody scFv (30 kDa) [197]	A potential therapeutic antibody for ras-derived tumors
	Anti-estradiol scFv (30 kDa) [186]	Evaluating the concentration of estradiol in urine or blood (for clinical examination and in the course of therapy) [198]
Recombinant vaccines	Hepatitis B virus pre-HBs antigen (30 kDa) [188]	Immunization against Hepatitis B
Others	α-Foetoprotein (74 kDa) [186]	As a therapeutic agent for autoimmune diseases [199]

Table 7. Production of nutraceuticals in *Y. lipolytica*

Category	Product	Therapeutic Application
Phenylpropanoids	Naringenin [200]	Neuroprotective and antioxidant [71]
	Eriodictyol [201]	Antioxidant and antiaging [71]
	Taxifolin [201]	Anticancer, Anti-inflammatory, and antidiabetic [71]
Inulin-type oligosaccharides	Fructooligosaccharides [31]	Remedy of traveler's diarrhea and irritable bowel syndrome [202], Adjustment of cholesterol profile, improving absorption of magnesium in postmenopausal women [203]
Fatty acids	γ-linolenic acid [62]	Treatment of inflammatory conditions [204]
	Eicosapentaenoic acid (EPA)	Treatment of heart-related disorders as well as reducing serum triglyceride (TG) and non-high-density lipoprotein cholesterol (non-HDL-C) levels and possibly decreasing main factors affecting atherogenesis [205]
	Arachidonic acid [206]	Essential for the activity of all cells, particularly in the immune system, nervous system, and skeletal muscles [207]
Lipids	Sterols [208]	Treatment of hypercholesterolemia [209]
Pigments	Carotenoids [210]	Reducing the risk of numerous ailments, predominantly eye diseases and certain cancers, as a result of their function as antioxidants [211]
Terpenoids	Lycopene [61, 212]	Anticancer [156], Antioxidant [157], Antidiabetic [158], anti aging [159]
	α-Santalene [213]	Antibacterial and diuretic [71]
	Limonene [214]	Antibacterial and insecticide [71]
	[+]-Nootkatone [215]	Anti-platelet aggregation and antiproliferative [71]
	Protopanaxadiol [216]	Anticancer, Antibiotic, Antiviral, and antitumor [71]
	Campesterol [217]	Anti-inflammatory [71]
	Ginsenoside K [218]	Anti-inflammatory and antitumor[71]
	Astaxanthin [219]	Antioxidant [71]
Sugar alcohol (polyol)	Erythritol [220-228]	An appropriate sugar replacement for diabetic people [228]
	Mannitol [221, 222, 229-235]	A sweetener in diabetic food, As a medication to decrease high pressures in the eyes, for assertive cases of kidney failure, for removal of toxins, and to treat fluid imbalances [236]
	Arabitol [233, 235, 237]	Anticarcinogenic agent, Adipose tissue reducer [185]

fore, a *P. pastoris*-expressed SARS-CoV recombinant RBD vaccine named BECOV2 was produced by Texas Children's Center for Vaccine Development at Baylor College of Medicine (TCH-CVD) in corporation with Biological E [89-92], and phase I/II clinical trial was initiated in India in November 2020 [93].

Besides, SpyBiotech and the Serum Institute of India have produced a novel virus-like particle vaccine named SIIPL, and it was dosed as the first subject in phase I/II clinical trials. All recombinant parts of the SIIPL vaccine were generated in yeast [94].

A platform for SARS-CoV-2 virus cloning

During the COVID-19 pandemic, a suitable host is needed for the genetic manipulation of the virus using recombinant DNA techniques. This manipulation achieves many goals, such as developing diagnostics in vivo models, antiviral therapeutics, and vaccines. Based on a recent investigation [95], *S. cerevisiae* was a suitable host for assembly and maintenance of RNA virus genomes, including SARS-CoV-2. *S. cerevisiae* exploits an inherently homologous recombination system called transformation-associated recombination (TAR) cloning, which makes it a good host to generate full-length

molecular clones from large DNA viruses such as coronaviruses [96].

TAR cloning application for assembly of full-length coronavirus cDNA has many advantages, such as reducing the time required to produce clones, providing a rapid method for genome engineering, and preparing an easy-to-use technique for establishment in different lab settings [97].

Recombinant tropane alkaloids

Tropane alkaloids (TA), derived from nightshade plants, are a valuable class of alkaloids widely used as neurotransmitter inhibitor drugs to treat several neuromuscular disorders. Accordingly, the World Health Organization (WHO) has classified them as necessary medications [98, 99]. Supplying these essential drugs can be jeopardized due to the recent pandemic caused by SARS-CoV-2 [100, 101]. Therefore, cost-effective production strategies using microbial cultures such as yeasts become crucial [102]. In this regard, a recent study has manipulated *S. cerevisiae* to produce medicinal alkaloids named hyoscyamine and scopolamine [103].

Conclusion

Modern biotechnology has led to new recombinant products such as biopharmaceuticals and nutraceuticals. These products can be used in a broad range of diseases, and there has been a global surge in demand for them in recent years. According to WHO, the speed of demographic aging is higher than before, and a wide range of the elderly population is concerned with many disorders like diabetes, different types of cancer, and chronic diseases. Therefore, the biopharmaceuticals market has expanded dramatically in the latest years, and this rising mode is anticipated to progress in the following years. In this regard, yeasts are one of the engineered hosts for the production of biopharmaceuticals. Scientists have modified the yeast system, making it more effective in creating roughly humanized protein. Non-conventional yeast systems, such as *P. pastoris*, were developed alongside *S. cerevisiae* to increase the yield of heterologous proteins. By upgrading fermentation methods and expression systems and incorporating synthetic biology approaches, we can successfully create many processes of producing recombinant proteins in yeast from start to finish. The advancements in glycan design enable the creation of humanized molecules with longer half-lives and lower immunogenicity. Further novel construction strategies must be employed in the yeast system's synthesis and secretory processes to manufacture therapeutic protein.

On the other hand, during the COVID-19 outbreak, high manufacturing capacity is required to provide life-saving medical supplies such as medicines and vaccines. Thus, yeast hosts can be very productive for the mass production of COVID-19 therapeutics based on their numerous capabilities. In addition, the development of diagnostic and therapeutic strategies requires a suitable host for manipulating the virus genome, and yeast hosts can also meet this demand.

Finally, according to the available data, there have not been any reviews concerning the usage of yeast hosts for industrial manufacture of FDA-approved pharmaceuticals and laboratory-scale production of nutraceuticals in recent years, mainly about COVID-19. Therefore, the present study can provide a good perspective on this issue.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

Conceptualization and supervision: Negar Mottaghi-Dastjerdi and Parastoo Tarighi; Investigation: Negar Mottaghi-Dastjerdi, Parastoo Tarighi, Farzane Arianfar and Seyedeh Mona Mousavi Esfahani; Writing the original draft: Negar Mottaghi-Dastjerdi, Parastoo Tarighi and Seyedeh Mona Mousavi Esfahani; Visualization and editing: Marjan Shariatpanahi; Reviewing: Negar Mottaghi-Dastjerdi.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Love KR, Dalvie NC, Love JC. The yeast stands alone: The future of protein biologic production. Curr Opin Biotechnol. 2018;5 3:50-8. [DOI: 10.1016/j.copbio.2017.12.010]

[2] Meehl MA, Stadheim TA. Biopharmaceutical discovery and production in yeast. Curr Opin Biotechnol. 2014; 30:120-7. [DOI:10.1016/j.copbio.2014.06.007] [PMID]

[3] Craik DJ, Fairlie DP, Liras S, Price D. The future of peptide-based drugs. Chem Biol Drug Des. 2013; 81(1):136-47. [DOI:10.1111/cbdd.12055] [PMID]

[4] Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies. Nat Rev Drug Discov. 2014; 13(9):655-72. [DOI:10.1038/nrd4363] [PMID] [PMCID]

[5] Gomes AR, Byregowda SM, Veeregowda BM, Balamurugan V. An overview of heterologous expression host systems for the production of recombinant proteins. Adv Anim Vet Sci. 2016. 4(4):346-56. [Link]

[6] Goodman M. Market watch: Sales of biologics to show robust growth through to 2013. Nat Rev Drug Discov. 2009; 8(11):837. [DOI:10.1038/nrd3040] [PMID]

[7] Lachance PA, Das YT. 1.11-Nutraceuticals. Comprehensive Medicinal Chemistry II. Reference Module in Chemistry, Molecular Sciences and Chemical Engineering. 2007; 1:449-61. [DOI:10.1016/B0-08-045044-X/00014-6]

[8] DeFelice SL. The nutraceutical revolution: Its impact on food industry R&D. Trends in Food Science & Technology. 1995; 6(2):59-61. [DOI:10.1016/S0924-2244(00)88944-X]

[9] Rajasekaran A.1.05 - Nutraceuticals. Reference Module in Chemistry, Molecular Sciences and Chemical Engineering. 2017; 107-34. [DOI:10.1016/B978-0-12-409547-2.12287-5]

[10] Komala MG, Ong SG, Qadri MU, Elshafie LM, Pollock CA, Saad S. Investigating the regulatory process, safety, efficacy and product transparency for nutraceuticals in the USA, Europe and Australia. Foods. 2023; 16:12(2):427. [DOI:10.3390/foods12020427]

[11] Chae HJ, Joo H, In MJ. Utilization of brewer's yeast cells for the production of food-grade yeast extract. Part 1: Effects of different enzymatic treatments on solid and protein recovery and flavor characteristics. Bioresour Technol. 2001; 76(3):253-8. [DOI:10.1016/S0960-8524(00)00102-4] [PMID]

[12] Ferreira I, Pinho O, Vieira E, Tavarela JG. Brewer's Saccharomyces yeast biomass: Characteristics and potential applications. Trends in Food Science & Technology. 2010; 21(2):77-84. [DOI:10.1016/j.tifs.2009.10.008]

[13] Gaudreau H, Renard N, Champagne CP, Van Horn D. The evaluation of mixtures of yeast and potato extracts in growth media for biomass production of lactic cultures. Can J Microbiol. 2002; 48(7):626-34. [DOI:10.1139/w02-052] [PMID]

[14] Li X, Li Z, Zheng J, Shi Z, Li L. Yeast extract promotes phase shift of bio-butanol fermentation by Clostridium acetobutylicum ATCC824 using cassava as substrate. Bioresour Technol. 2012; 125:43-51. [DOI:10.1016/j.biortech.2012.08.056]

[15] Boroumand Moghaddam A, Namvar F, Moniri M, Md Tahir P, Azizi S, Mohamad R. Nanoparticles biosynthesized by fungi and yeast: A review of their preparation, properties, and medical applications. Molecules. 2015; 20(9):16540-65. [DOI:10.3390/molecules200916540] [PMID] [PMCID]

[16] Plasson C, Michel R, Lienard D, Saint-Jore-Dupas C, Sourrouille C, March GGd, et al. Production of recombinant proteins in suspension-cultured plant cells. Methods Mol Biol. 2009; 483:145-61. [DOI:10.1007/978-1-59745-407-0_9] [PMID]

[17] Wurm FM. Production of recombinant protein therapeutics in cultivated mammalian cells. Nat Biotechnol. 2004; 22(11):1393-8. [DOI:10.1038/nbt1026] [PMID]

[18] Ward OP. Production of recombinant proteins by filamentous fungi. Biotechnol Adv. 2012; 30(5):1119-39. [DOI:10.1016/j.biotechadv.2011.09.012] [PMID]

[19] Ikonomou L, Schneider YJ, Agathos SN. Insect cell culture for industrial production of recombinant proteins. Appl Microbiol Biotechnol. 2003; 62(1):1-20. [DOI:10.1007/s00253-003-1223-9] [PMID]

[20] Mattanovich D, Branduardi P, Dato L, Gasser B, Sauer M, Porro D. Recombinant protein production in yeasts. Methods Mol Biol. 2012; 824:329-58. [DOI:10.1007/978-1-61779-433-9_17] [PMID]

[21] Lasserre JP, Dautant A, Aiyar RS, Kucharczyk R, Glatigny A, Tribouillard-Tanvier D, et al. Yeast as a system for modeling mitochondrial disease mechanisms and discovering therapies. Dis Model Mech. 2015; 8(6):509-26. [DOI:10.1242/dmm.020438] [PMID] [PMCID]

[22] Becker B, Schnöder T, Schmitt MJ. Yeast reporter assay to identify cellular components of ricin toxin a chain trafficking. Toxins. 2016; 8(12):366. [DOI:10.3390/toxins8120366] [PMID] [PMCID]

[23] Diehl B, Hoffmann TM, Mueller NC, Burkhart JL, Kazmaier U, Schmitt MJ. Novel yeast bioassay for high-throughput screening of matrix metalloproteinase inhibitors. Appl Environ Microbiol. 2011; 77(24):8573-7. [DOI:10.1128/AEM.06111-11] [PMID] [PMCID]

[24] Fernández-Acero T, Rodríguez-Escudero I, Vicente F, Monteiro MC, Tormo JR, Cantizani J, et al. A yeast-based in vivo bioassay to screen for class I phosphatidylinositol 3-kinase specific inhibitors. J Biomol Screen. 2012; 17(8):1018-29. [DOI:10.1177/1087057112450051] [PMID]

[25] Mohamad UH, Hamid UMA, Abdullah MF. Development of a yeast bioassay for the screening of anti-malarial compounds with artemisinin-like activities. Paper presented at: 2012 IEEE Colloquium on Humanities, Science and Engineering (CHUSER). 03-04 December 2012; Kota Kinabalu, Malaysia. [DOI:10.1109/CHUSER.2012.6504294]

[26] Chernoff YO. Stress and prions: Lessons from the yeast model. FEBS Lett. 2007; 581(19):3695-701. [DOI:10.1016/j.febslet.2007.04.075] [PMID] [PMCID]

[27] Ter-Avanesyan MD, Dagkesamanskaya AR, Kushnirov VV, Smirnov VN. The SUP35 omnipotent suppressor gene is involved in the maintenance of the non-Mendelian determinant [psi+] in the yeast Saccharomyces cerevisiae. Genetics. 1994; 137(3):671-6. [DOI:10.1093/genetics/137.3.671] [PMID] [PMCID]

[28] Bach S, Talarek N, Andrieu T, Vierfond JM, Mettey Y, Galons H, et al. Isolation of drugs active against mammalian prions using a yeast-based screening assay. Nat Biotechnol. 2003; 21(9):1075-81. [DOI:10.1038/nbt855] [PMID]

[29] Bach S, Tribouillard D, Talarek N, Desban N, Gug F, Galons H, et al. A yeast-based assay to isolate drugs active against mammalian prions. Methods. 2006; 39(1):72-7. [DOI:10.1016/j.ymeth.2006.04.005] [PMID]

[30] Rodriguez A, Strucko T, Stahlhut SG, Kristensen M, Svenssen DK, Forster J, et al. Metabolic engineering of yeast for fermentative production of flavonoids. Bioresour Technol. 2017; 245(Pt B):1645-54. [DOI:10.1016/j.biortech.2017.06.043] [PMID]

[31] Han YZ, Zhou CC, Xu YY, Yao JX, Chi Z, Chi ZM, et al. High-efficient production of fructo-oligosaccharides from inulin by a two-stage bioprocess using an engineered Yarrowia lipolytica strain. Carbohydr Polym. 2017; 173:592-9. [DOI:10.1016/j.carbpol.2017.06.043] [PMID]

[32] Li M, Schneider K, Kristensen M, Borodina I, Nielsen J. Engineering yeast for high-level production of stilbenoid antioxidants. Sci Rep. 2016; 6:36827. [DOI:10.1038/srep36827] [PMID] [PMCID]

[33] Koopman F, Beekwilder J, Crimi B, van Houwelingen A, Hall RD, Bosch D, et al. De novo production of the flavonoid naringenin in engineered Saccharomyces cerevisiae. Microb Cell Fact. 2012; 11:155. [DOI:10.1186/1475-2859-11-155] [PMID] [PMCID]

[34] Li M, Kildegaard KR, Chen Y, Rodriguez A, Borodina I, Nielsen J. De novo production of resveratrol from glucose or ethanol by engineered Saccharomyces cerevisiae. Metab Eng. 2015; 32:1-11. [PMID]

[35] Ma T, Shi B, Ye Z, Li X, Liu M, Chen Y, et al. Lipid engineering combined with systematic metabolic engineering of Saccharomyces cerevisiae for high-yield production of lycopene. Metab Eng. 2019; 52:134-42. [DOI:10.1016/j.ymben.2018.11.009] [PMID]

[36] Jin J, Wang Y, Yao M, Gu X, Li B, Liu H, et al. Astaxanthin overproduction in yeast by strain engineering and new gene target uncovering. Biotechnol Biofuels. 2018; 11:230. [DOI:10.1186/s13068-018-1227-4] [PMID] [PMCID]

[37] Çelik E, Çalık P. Production of recombinant proteins by yeast cells. Biotechnol Adv. 2012; 30(5):1108-18. [DOI:10.1016/j.biotechadv.2011.09.011] [PMID]

[38] Puxbaum V, Mattanovich D, Gasser B. Quo vadis? The challenges of recombinant protein folding and secretion in Pichia pastoris. Appl Microbiol Biotechnol. 2015; 99(7):2925-38. [DOI:10.1007/s00253-015-6470-z] [PMID]

[39] Cereghino JL, Cregg JM. Heterologous protein expression in the methylotrophic yeast Pichia pastoris. FEMS Microbiol Rev. 2000; 24(1):45-66. [DOI:10.1111/j.1574-6976.2000.tb00532.x] [PMID]

[40] Weinhandl K, Winkler M, Glieder A, Camattari A. Carbon source dependent promoters in yeasts. Microb Cell Fact. 2014; 13:5. [DOI:10.1186/1475-2859-13-5] [PMID] [PMCID]

[41] Gasser B, Steiger MG, Mattanovich D. Methanol regulated yeast promoters: Production vehicles and toolbox for synthetic biology. Microb Cell Fact. 2015; 14:196. [DOI:10.1186/s12934-015-0387-1] [PMID] [PMCID]

[42] Heyland J, Fu J, Blank LM, Schmid A. Quantitative physiology of Pichia pastoris during glucose-limited high-cell density fed-batch cultivation for recombinant protein production. Biotechnol Bioeng. 2010; 107(2):357-68. [DOI:10.1002/bit.22836] [PMID]

[43] Ergün BG, Çalık P. Lignocellulose degrading extremozymes produced by Pichia pastoris: Current status and future prospects. Bioprocess Biosyst Eng. 2016; 39(1):1-36. [DOI:10.1007/s00449-015-1476-6] [PMID]

[44] Juturu V, Wu JC. Heterologous protein expression in Pichia pastoris: Latest research progress and applications. Chembiochem. 2018; 19(1):7-21. [DOI:10.1002/cbic.201700460] [PMID]

[45] Li P, Anumanthan A, Gao XG, Ilangovan K, Suzara VV, Düzgüneş N, et al. Expression of recombinant proteins in Pichia pastoris. Appl Biochem Biotechnol. 2007; 142(2):105-24. [DOI:10.1007/s12010-007-0003-x] [PMID]

[46] Macauley-Patrick S, Fazenda ML, McNeil B, Harvey LM. Heterologous protein production using the Pichia pastoris expression system. Yeast. 2005; 22(4):249-70. [DOI:10.1002/yea.1208] [PMID]

[47] Looser V, Bruhlmann B, Bumbak F, Stenger C, Costa M, Camattari A, et al. Cultivation strategies to enhance productivity of Pichia pastoris: A review. Biotechnol Adv. 2015; 33(6 Pt 2):1177-93. [DOI:10.1016/j.biotechadv.2015.05.008] [PMID]

[48] Potvin G, Ahmad A, Zhang Z. Bioprocess engineering aspects of heterologous protein production in Pichia pastoris: A review. Biochem Eng J. 2012; 64:91-105. [DOI:10.1016/j.bej.2010.07.017]

[49] Radecka D, Mukherjee V, Mateo RQ, Stojiljkovic M, Foulquié-Moreno MR, Thevelein JM. Looking beyond Saccharomyces: The potential of non-conventional yeast species for desirable traits in bioethanol fermentation. FEMS Yeast Res. 2015; 15(6):fov053. [DOI:10.1093/femsyr/fov053] [PMID]

[50] Hartner FS, Glieder A. Regulation of methanol utilisation pathway genes in yeasts. Microb Cell Fact. 2006; 5:39. [DOI:10.1186/1475-2859-5-39] [PMID] [PMCID]

[51] van Dijk R, Faber KN, Kiel JA, Veenhuis M, van der Klei I. The methylotrophic yeast Hansenula polymorpha: A versatile cell factory. Enzyme Microb Technol. 2000; 26(9-10):793-800. [DOI:10.1016/S0141-0229(00)00173-3] [PMID]

[52] Mayer AF, Hellmuth K, Schlieker H, Lopez-Ulibarri R, Oertel S, Dahlems U, et al. An expression system matures: A highly efficient and cost-effective process for phytase production by recombinant strains of Hansenula polymorpha. Biotechnol Bioeng. 1999; 63(3):373-81. [PMID]

[53] Veenhuis M, Kram AM, Kunau WH, Harder W. Excessive membrane development following exposure of the methylotrophic yeast Hansenula polymorpha to oleic acid-containing media. Yeast. 1990; 6(6):511-9. [DOI:10.1002/yea.320060608]

[54] Baerends RJ, Faber KN, Kram AM, Kiel JA, van der Klei IJ, Veenhuis M. A stretch of positively charged amino acids at the N terminus ofhansenula polymorpha Pex3p is involved in incorporation of the protein into the peroxisomal membrane. J Biol Chem. 2000; 275(14):9986-95. [DOI:10.1074/jbc.275.14.9986] [PMID]

[55] Gellissen G. Hansenula polymorpha: Biology and applications. New Jersey: Wiley; 2002. [DOI:10.1002/3527602356]

[56] Agaphonov MO, Romanova NV, Trushkina PM, Smirnov VN, Ter-Avanesyan MD. Aggregation and retention of human urokinase type plasminogen activator in the yeast endoplasmic reticulum. BMC Mol Biol. 2002; 3:15. [DOI:10.1186/1471-2199-3-15] [PMID] [PMCID]

[57] Müller II F, Tieke A, Waschk D, Mühle C, Müller F, Seigelchifer M, et al. Production of IFNα-2a in hansenula polymorpha. Process Biochem. 2002; 38(1):15-25. [DOI:10.1016/S0032-9592(02)00037-7]

[58] Suckow M, Gellissen G. The expression platform based on H. polymorpha strain RB11 and its derivatives-history, status and perspectives. In: Gellissen G, editor. Hansenula polymorpha: Biology and applications. New Jersey: Wiley; 2002. [Link]

[59] Coelho M, Amaral P, Belo I. Yarrowia lipolytica: An industrial workhorse. In: Méndez-Vilas A (editor). Current research, technology and education topics in applied microbiology and microbial biotechnology. Badajoz: Formatex Research Center; 2010. [Link]

[60] Matthäus F, Ketelhot M, Gatter M, Barth G. Production of lycopene in the non-carotenoid-producing yeast Yarrowia lipolytica. Appl Environ Microbiol. 2014; 80(5):1660-9. [DOI:10.1128/AEM.03167-13] [PMID] [PMCID]

[61] Schwartz C, Frogue K, Misa J, Wheeldon I. Host and pathway engineering for enhanced lycopene biosynthesis in Yarrowia lipolytica. Front Microbiol. 2017; 8:2233. [DOI:10.3389/fmicb.2017.02233] [PMID] [PMCID]

[62] Sun ML, Madzak C, Liu HH, Song P, Ren LJ, Huang H, et al. Engineering Yarrowia lipolytica for efficient γ-linolenic acid production. Biochem Eng J. 2017; 117(A):172-80. [DOI:10.1016/j.bej.2016.10.014]

[63] Xue Z, Sharpe PL, Hong SP, Yadav NS, Xie D, Short DR, et al. Production of omega-3 eicosapentaenoic acid by metabolic engineering of Yarrowia lipolytica. Nat Biotechnol. 2013; 31(8):734-40. [DOI:10.1038/nbt.2622] [PMID]

[64] Kim H, Yoo SJ, Kang HA. Yeast synthetic biology for the production of recombinant therapeutic proteins. FEMS Yeast Res. 2015; 15(1):1-16. [DOI:10.1111/1567-1364.12195] [PMID]

[65] Jadhav VV, Salunkhe DS, Bhadekar RK. Effect of alterations in conventional medium on lipid accumulation and fatty acid content in oleaginous yeasts. Int J Pharm Bio Sci. 2012; 3(4):757-69. [Link]

[66] Martínez JL, Liu L, Petranovic D, Nielsen J. Pharmaceutical protein production by yeast: Towards production of human blood proteins by microbial fermentation. Curr Opin Biotechnol. 2012; 23(6):965-71. [DOI:10.1016/j.copbio.2012.03.011] [PMID]

[67] Muñoz P, Bouza E, Cuenca-Estrella M, Eiros JM, Pérez MJ, Sánchez-Somolinos M, et al. Saccharomyces cerevisiae fungemia: An emerging infectious disease. Clin Infect Dis. 2005; 40(11):1625-34. [DOI:10.1086/429916] [PMID]

[68] Yang EJ, Park GH, Song KS. Neuroprotective effects of liquiritigenin isolated from licorice roots on glutamate-induced apoptosis in hippocampal neuronal cells. Neurotoxicology. 2013; 39:114-23. [DOI:10.1016/j.neuro.2013.08.012] [PMID]

[69] Borodina I, Nielsen J. Advances in metabolic engineering of yeast Saccharomyces cerevisiae for production of chemicals. Biotechnol J. 2014; 9(5):609-20. [DOI:10.1002/biot.201300445] [PMID]

[70] Ahmad M, Hirz M, Pichler H, Schwab H. Protein expression in Pichia pastoris: Recent achievements and perspectives for heterologous protein production. Appl Microbiol Biotechnol. 2014; 98(12):5301-17. [DOI:10.1007/s00253-014-5732-5] [PMID] [PMCID]

[71] Chen R, Yang S, Zhang L, Zhou YJ. Advanced strategies for production of natural products in yeast. iScience. 2020; 23(3):100879. [DOI:10.1016/j.isci.2020.100879] [PMID] [PMCID]

[72] Manfrão-Netto JHC, Gomes AMV, Parachin NS. Advances in using Hansenula polymorpha as Chassis for Recombinant Protein Production. Front Bioeng Biotechnol. 2019; 7:94. [DOI:10.3389/fbioe.2019.00094] [PMID] [PMCID]

[73] Galanie S, Thodey K, Trenchard IJ, Filsinger Interrante M, Smolke CD. Complete biosynthesis of opioids in yeast. Science. 2015; 349(6252):1095-100. [DOI:10.1126/science.aac9373] [PMID] [PMCID]

[74] Li Y, Li S, Thodey K, Trenchard I, Cravens A, Smolke CD. Complete biosynthesis of noscapine and halogenated alkaloids in yeast. Proc Natl Acad Sci U S A. 2018; 115(17):E3922-E31. [DOI:10.1073/pnas.1721469115] [PMID] [PMCID]

[75] Madzak C, Tréton B, Blanchin-Roland S. Strong hybrid promoters and integrative expression/secretion vectors for quasi-constitutive expression of heterologous proteins in the yeast Yarrowia lipolytica. J Mol Microbiol Biotechnol. 2000; 2(2):207-16. [PMID]

[76] Zhao J, Zhao S, Ou J, Zhang J, Lan W, Guan W, et al. COVID-19: Coronavirus vaccine development updates. Front Immunol. 2020; 11:602256. [DOI:10.3389/fimmu.2020.602256] [PMID] [PMCID]

[77] Izda V, Jeffries MA, Sawalha AH. COVID-19: A review of therapeutic strategies and vaccine candidates. Clin Immunol. 2021; 222:108634. [DOI:10.1016/j.clim.2020.108634] [PMID] [PMCID]

[78] Nielsen KH. Protein expression-yeast. Methods Enzymol. 2014; 536:133-47. [DOI:10.1016/B978-0-12-420070-8.00012-X] [PMID]

[79] Hansson M, Nygren PA, Ståhl S. Design and production of recombinant subunit vaccines. Biotechnol Appl Biochem. 2000; 32(2):95-107. [DOI:10.1042/BA20000034] [PMID]

[80] Choi J, Kim MG, Oh YK, Kim YB. Progress of Middle East respiratory syndrome coronavirus vaccines: A patent review. Expert Opin Ther Pat. 2017; 27(6):721-31. [DOI:10.1080/13543776.2017.1281248] [PMID]

[81] Okba NM, Raj VS, Haagmans BL. Middle East respiratory syndrome coronavirus vaccines: Current status and novel approaches. Curr Opin Virol. 2017; 23:49-58. [DOI:10.1016/j.coviro.2017.03.007] [PMID] [PMCID]

[82] Li J, Ulitzky L, Silberstein E, Taylor DR, Viscidi R. Immunogenicity and protection efficacy of monomeric and trimeric recombinant SARS coronavirus spike protein subunit vaccine candidates. Viral Immunol. 2013; 26(2):126-32. [DOI:10.1089/vim.2012.0076] [PMID] [PMCID]

[83] He Y, Li J, Heck S, Lustigman S, Jiang S. Antigenic and immunogenic characterization of recombinant baculovirus-expressed severe acute respiratory syndrome coronavirus spike protein: Implication for vaccine design. J Virol. 2006; 80(12):5757-67. [DOI:10.1128/JVI.00083-06] [PMID] [PMCID]

[84] Kam YW, Kien F, Roberts A, Cheung YC, Lamirande EW, Vogel L, et al. Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcγRII-dependent entry into B cells in vitro. Vaccine. 2007; 25(4):729-40. [DOI:10.1016/j.vaccine.2006.08.011] [PMID] [PMCID]

[85] He Y, Zhou Y, Liu S, Kou Z, Li W, Farzan M, et al. Receptor-binding domain of SARS-CoV spike protein induces highly potent neutralizing antibodies: Implication for developing subunit vaccine. Biochem Biophys Res Commun. 2004; 324(2):773-81. [DOI:10.1016/j.bbrc.2004.09.106] [PMID] [PMCID]

[86] Du L, Zhao G, Li L, He Y, Zhou Y, Zheng BJ, et al. Antigenicity and immunogenicity of SARS-CoV S protein receptor-binding domain stably expressed in CHO cells. Biochem Biophys Res Commun. 2009; 384(4):486-90. [DOI:10.1016/j.bbrc.2009.05.003] [PMID] [PMCID]

[87] Du L, Zhao G, Chan CC, Sun S, Chen M, Liu Z, et al. Recombinant receptor-binding domain of SARS-CoV spike protein expressed in mammalian, insect and E. coli cells elicits potent neutralizing antibody and protective immunity. Virology. 2009; 393(1):144-50. [DOI:10.1016/j.virol.2009.07.018] [PMID] [PMCID]

[88] Argentinian AntiCovid Consortium. Structural and functional comparison of SARS-CoV-2-spike receptor binding domain produced in Pichia pastoris and mammalian cells. Sci Rep. 2020; 10(1):21779. [DOI:10.1038/s41598-020-78711-6] [PMID] [PMCID]

[89] Pollet J, Chen WH, Versteeg L, Keegan B, Zhan B, Wei J, et al. SARSCoV-2 RBD219-N1C1: A yeast-expressed sars-cov-2 recombinant receptor-binding domain candidate vaccine stimulates virus neutralizing antibodies and T-cell immunity in mice. Hum Vaccin Immunother. 2021; 17(8):2356-66. [DOI:10.1101/2020.11.04.367359]

[90] Chen WH, Tao X, Agrawal AS, Algaissi A, Peng BH, Pollet J, et al. Yeast-expressed SARS-CoV recombinant receptor-binding domain (RBD219-N1) formulated with aluminum hydroxide induces protective immunity and reduces immune enhancement. Vaccine. 2020; 38(47):7533-41. [DOI:10.1016/j.vaccine.2020.09.061] [PMID] [PMCID]

[91] Chen WH, Wei J, Kundu RT, Adhikari R, Liu Z, Lee J, et al. Cloning, expression and biophysical characterization of a yeast-expressed recombinant SARS-CoV-2 receptor binding domain COVID-19 vaccine candidate. bioRxiv. 2020; 1-28. [DOI:10.1101/2020.11.09.373449]

[92] No Author. Coronavirus | U.S.-based Baylor College of Medicine ties up with India's Biological E for COVID-19 vaccine [Internet]. 2020 [Updated 2020 August 28]. Availble from: [Link]

[93] Biological E. Limited Starts Phase I/II Clinical Trial of its COVID-19 Vaccine Candidate [Internet]. 2020 [Updated 2020 November 16]. Availble from: [Link]

[94] Sharifzadeh M, Mottaghi-Dastjerdi N, Soltany Rezae Raad M. A review of virus-like particle-based SARS-CoV-2 vaccines in clinical trial phases. Iran J Pharm Res. 2022; 21(1):e127042. [DOI:10.5812/ijpr-127042] [PMID] [PMCID]

[95] Koch L. A platform for RNA virus cloning. Nature Reviews Genetics. 2020:1-. [DOI:10.1038/s41576-020-0246-8] [PMID] [PMCID]

[96] Thi Nhu Thao T, Labroussaa F, Ebert N, V'kovski P, Stalder H, Portmann J, et al. Rapid reconstruction of SARS-CoV-2 using a synthetic genomics platform. Nature. 2020; 582(7813):561-5. [DOI:10.1038/s41586-020-2294-9] [PMID]

[97] Thao TTN, Labroussaa F, Ebert N, Jores J, Thiel V. In-yeast assembly of coronavirus infectious cDNA clones using a synthetic genomics pipeline. Methods Mol Biol. 2020; 2203:167-84. [DOI:10.1007/978-1-0716-0900-2_13] [PMID]

[98] Grynkiewicz G, Gadzikowska M. Tropane alkaloids as medicinally useful natural products and their synthetic derivatives as new drugs. Pharmacol Rep. 2008; 60(4):439-63. [PMID]

[99] World Health Organization. The selection and use of essential medicines: Report of the WHO Expert Committee, 2015 (including the 19th WHO model list of essential medicines and the 5th WHO model list of essential medicines for children). Geneva: World Health Organization; 2015. [Link]

[100] Gehrie EA, Frank SM, Goobie SM. Balancing supply and demand for blood during the COVID-19 pandemic. Anesthesiology. 2020;133(1):16-8. [DOI:10.1097/ALN.0000000000003341] [PMID]

[101] American Society of Anesthesiologists. ASA Urges Federal Government to Take Action on Drug Shortages. Illinois: American Society of Anesthesiologists; 2020. [Link]

[102] Kohnen-Johannsen KL, Kayser O. Tropane alkaloids: Chemistry, pharmacology, biosynthesis and production. Molecules. 2019; 24(4):796. [DOI:10.3390/molecules24040796] [PMID] [PMCID]

[103] Srinivasan P, Smolke CD. Engineering a microbial biosynthesis platform for de novo production of tropane alkaloids. Nat Commun. 2019; 10(1):3634. [DOI:10.1038/s41467-019-11588-w] [PMID] [PMCID]

[104] Carreras, Marc, Pere Ibern, José María Inoriza. Ageing and healthcare expenditures: Exploring the role of individual health status." Health Econ. (2018); 27(5):865-876. [DOI:10.1002/hec.3635] [PMID]

[105] Kesik-Brodacka M. Progress in biopharmaceutical development.Biotechnol Appl Biochem. 2018; 65(3):306-22. [DOI:10.1002/bab.1617] [PMID] [PMCID]

[106] Madhavan A, Arun KB, Sindhu R, Krishnamoorthy J, Reshmy R, Sirohi R, et al. Customized yeast cell factories for biopharmaceuticals: From cell engineering to process scale up. Microb Cell Fact. 2021; 20(1):124. [DOI:10.1186/s12934-021-01617-z] [PMID] [PMCID]

[107] El-Baky NA, Redwan EM. Therapeutic alpha-interferons protein: Structure, production, and biosimilar. Preparative Biochemistry and Biotechnology. 2015; 45(2):109-27. [DOI:10.1080/10826068.2014.907175] [PMID]

[108] Albumedix Ltd. CBER FDA drug master file acceptance for Recombumin® Elite and appointment of director of regulatory affairs. Nottingham: Albumedix Ltd; 2020. [Link]

[109] Abdel-Samad N. Treatment with recombinant factor XIII (Tretten) in a pregnant woman with factor XIII deficiency. American J Case Rep. 2017; 18:436. [DOI:10.12659/AJCR.901502] [PMID]

[110] Raedler LA. Tresiba (insulin degludec injection) and Ryzodeg 70/30 (insulin degludec and insulin aspart injection): Two new insulin analogs for glycemic control in diabetes mellitus. Am Health Drug Benefits. 2016; 9(Spec Feature):144-8. [PMID]

[111] European Medicines Agency. Somatropin biopartners. Amsterdam: European Medicines Agency; 2013. [Link]

[112] No Author. AUGMENT® bone graft. Memphis: Wright Medical Technology, Inc. [Link]

[113] No Author. AUGMENT® injectable package insert. Memphis: Wright Medical Technology, Inc.; 2018. [Link]

[114] Bow A, Anderson DE, Dhar M. Commercially available bone graft substitutes: The impact of origin and processing on graft functionality. Drug Metab Rev. 2019; 51(4):533-44. [DOI:10.1080/03602532.2019.1671860] [PMID]

[115] Casares S, Brumeanu TD, Richie TL. The RTS, S malaria vaccine. Vaccine. 2010; 28(31):4880-94. [DOI:10.1016/j.vaccine.2010.05.033] [PMID]

[116] Cooper MM, Loiseau C, McCarthy JS, Doolan DL. Human challenge models: Tools to accelerate the development of malaria vaccines. Expert Rev Vaccines. 2019; 18(3):241-51. [DOI:10.1080/14760584.2019.1580577] [PMID]

[117] Gonçalves D, Lima C, Ferreira P, Costa P, Costa A, Figueiredo W, et al. Orange juice as dietary source of antioxidants for patients with Hepatitis C under antiviral therapy. Food Nutr Res. 2017; 61(1):1296675. [DOI:10.1080/16546628.2017.1296675] [PMID] [PMCID]

[118] Da Pozzo E, Costa B, Cavallini C, Testai L, Martelli A, Calderone V, et al. The citrus flavanone naringenin protects myocardial cells against age-associated damage. Oxid Med Cell Longev. 2017; 2017:9536148. [DOI:10.1155/2017/9536148] [PMID] [PMCID]

[119] Jung SK, Ha SJ, Jung CH, Kim YT, Lee HK, Kim MO, et al. Naringenin targets ERK 2 and suppresses UVB-induced photoaging. J Cell Mol Med. 2016; 20(5):909-19. [DOI:10.1111/jcmm.12780] [PMID] [PMCID]

[120] Zhang Y, Liu B, Chen X, Zhang N, Li G, Zhang LH, et al. Naringenin ameliorates behavioral dysfunction and neurological deficits in a d-galactose-induced aging mouse model through activation of PI3K/Akt/Nrf2 pathway. Rejuvenation Res. 2017; 20(6):462-72. [DOI:10.1089/rej.2017.1960] [PMID]

[121] Ghofrani S, Joghataei MT, Mohseni S, Baluchnejadmojarad T, Bagheri M, Khamse S, et al. Naringenin improves learning and memory in an Alzheimer's disease rat model: Insights into the underlying mechanisms. Eur J Pharmacol. 2015; 764:195-201. [DOI:10.1016/j.ejphar.2015.07.001] [PMID]

[122] Seyedrezazadeh E, Kolahian S, Shahbazfar AA, Ansarin K, Pour Moghaddam M, Sakhinia M, et al. Effects of the flavanone combination hesperetin-naringenin, and orange and grapefruit juices, on airway inflammation and remodeling in a murine asthma model. Phytother Res. 2015; 29(4):591-8. [DOI:10.1002/ptr.5292] [PMID]

[123] Ke JY, Banh T, Hsiao YH, Cole RM, Straka SR, Yee LD, et al. Citrus flavonoid naringenin reduces mammary tumor cell viability, adipose mass, and adipose inflammation in obese ovariectomized mice. Mol Nutr Food Res. 2017; 61(9):1600934. [DOI:10.1002/mnfr.201600934] [PMID]

[124] Al-Rejaie SS, Aleisa AM, Abuohashish HM, Parmar MY, Ola MS, Al-Hosaini AA, et al. Naringenin neutralises oxidative stress and nerve growth factor discrepancy in experimental diabetic neuropathy. Neurol Res. 2015; 37(10):924-33. [DOI:10.1179/1743132815Y.0000000079] [PMID]

[125] Al-Dosari DI, Ahmed MM, Al-Rejaie SS, Alhomida AS, Ola MS. Flavonoid naringenin attenuates oxidative stress, apoptosis and improves neurotrophic effects in the diabetic rat retina. Nutrients. 2017; 9(10):1161. [DOI:10.3390/nu9101161] [PMID] [PMCID]

[126] Sandeep M, Nandini C. Influence of quercetin, naringenin and berberine on glucose transporters and insulin signalling molecules in brain of streptozotocin-induced diabetic rats. Biomed Pharmacother. 2017; 94:605-611. [DOI:10.1016/j.biopha.2017.07.142] [PMID]

[127] Ren B, Qin W, Wu F, Wang S, Pan C, Wang L, et al. Apigenin and naringenin regulate glucose and lipid metabolism, and ameliorate vascular dysfunction in type 2 diabetic rats. Eur J Pharmacol. 2016; 773:13-23. [DOI:10.1016/j.ejphar.2016.01.002] [PMID]

[128] Roy S, Ahmed F, Banerjee S, Saha U. Naringenin ameliorates streptozotocin-induced diabetic rat renal impairment by downregulation of TGF-β1 and IL-1 via modulation of oxidative stress correlates with decreased apoptotic events. Pharm Biol. 2016; 54(9):1616-27. [PMID]

[129] Wang LH, Wang MS, Zeng XA, Xu XM, Brennan CS. Membrane and genomic DNA dual-targeting of citrus flavonoid naringenin against Staphylococcus aureus. Integr Biol (Camb). 2017; 9(10):820-9. [DOI:10.1039/C7IB00095B] [PMID]

[130] Liang J, Halipu Y, Hu F, Yakeya B, Chen W, Zhang H, et al. Naringenin protects keratinocytes from oxidative stress injury via inhibition of the NOD2-mediated NF-κB pathway in pemphigus vulgaris. Biomed Pharmacother. 2017; 92:796-801. [DOI:10.1016/j.biopha.2017.05.112] [PMID]

[131] Malhotra A, Bath S, Elbarbry F. An organ system approach to explore the antioxidative, anti-inflammatory, and cytoprotective actions of resveratrol. Oxid Med Cell Longev. 2015; 2015:803971. [DOI:10.1155/2015/803971] [PMID] [PMCID]

[132] Kuršvietienė L, Stanevičienė I, Mongirdienė A, Bernatonienė J. Multiplicity of effects and health benefits of resveratrol. Medicina. 2016; 52(3):148-55. [DOI:10.1016/j.medici.2016.03.003] [PMID]

[133] Bishayee A. Cancer prevention and treatment with resveratrol: From rodent studies to clinical trials. Cancer Prev Res (Phila). 2009; 2(5):409-18. [DOI:10.1158/1940-6207.CAPR-08-0160] [PMID]

[134] Delucchi F, Berni R, Frati C, Cavalli S, Graiani G, Sala R, et al. Resveratrol treatment reduces cardiac progenitor cell dysfunction and prevents morpho-functional ventricular remodeling in type-1 diabetic rats. Plos One. 2012; 7(6):e39836. [DOI:10.1371/journal.pone.0039836] [PMID] [PMCID]

[135] Yan F, Sun X, Xu C. Protective effects of resveratrol improve cardiovascular function in rats with diabetes. Exp Ther Med. 2018; 15(2):1728-34. [DOI:10.3892/etm.2017.5537]

[136] Sun AY, Wang Q, Simonyi A, Sun GY. Resveratrol as a therapeutic agent for neurodegenerative diseases. Mol Neurobiol. 2010; 41(2-3):375-83. [DOI:10.1007/s12035-010-8111-y] [PMID] [PMCID]

[137] Dvorakova M, Landa P. Anti-inflammatory activity of natural stilbenoids: A review. Pharmacol Res. 2017; 124:126-45. [DOI:10.1016/j.phrs.2017.08.002] [PMID]

[138] Macler BA, Merkle JC. Current knowledge on groundwater microbial pathogens and their control. Hydrogeol J. 2000; 8(1):29. [DOI:10.1007/PL00010972]

[139] Markovic ZS, Mentus SV, Dimitrić Marković JM. Electrochemical and density functional theory study on the reactivity of fisetin and its radicals: Implications on in vitro antioxidant activity. J Phys Chem A. 2009; 113(51):14170-9. [DOI:10.1021/jp907071v] [PMID]

[140] Syed DN, Suh Y, Afaq F, Mukhtar H. Dietary agents for chemoprevention of prostate cancer. Cancer Lett. 2008; 265(2):167-76. [DOI:10.1016/j.canlet.2008.02.050] [PMID] [PMCID]

[141] Maher P, Akaishi T, Abe K. Flavonoid fisetin promotes ERK-dependent long-term potentiation and enhances memory. Proc Natl Acad Sci U S A. 2006; 103(44):16568-73. [DOI:10.1073/pnas.0607822103] [PMID] [PMCID]

[142] Liu X, Cheng J, Zhang G, Ding W, Duan L, Yang J, et al. Engineering yeast for the production of breviscapine by genomic analysis and synthetic biology approaches. Nat Commun. 2018; 9(1):448. [DOI:10.1038/s41467-018-02883-z] [PMID] [PMCID]

[143] Eichenberger M, Hansson A, Fischer D, Dürr L, Naesby M. De novo biosynthesis of anthocyanins in Saccharomyces cerevisiae. FEMS Yeast Res. 2018; 18(4). [DOI:10.1093/femsyr/foy046] [PMID]

[144] Eichenberger M, Lehka BJ, Folly C, Fischer D, Martens S, Simón E, et al. Metabolic engineering of Saccharomyces cerevisiae for de novo production of dihydrochalcones with known antioxidant, antidiabetic, and sweet tasting properties. Metab Eng. 2017; 39:80-89. [DOI:10.1016/j.ymben.2016.10.019] [PMID] [PMCID]

[145] Jiang J, Yin H, Wang S, Zhuang Y, Liu S, Liu T, et al. Metabolic engineering of Saccharomyces cerevisiae for high-level production of salidroside from glucose. J Agric Food Chem. 2018; 66(17):4431-8. [DOI:10.1021/acs.jafc.8b01272] [PMID]

[146] Trantas E, Panopoulos N, Ververidis F. Metabolic engineering of the complete pathway leading to heterologous biosynthesis of various flavonoids and stilbenoids in Saccharomyces cerevisiae. Metab Eng. 2009; 11(6):355-66. [DOI:10.1016/j.ymben.2009.07.004] [PMID]

[147] Lin MK, Yu YL, Chen KC, Chang WT, Lee MS, Yang MJ, et al. Kaempferol from Semen cuscutae attenuates the immune function of dendritic cells. Immunobiology. 2011; 216(10):1103-9. [DOI:10.1016/j.imbio.2011.05.002] [PMID]

[148] Chen AY, Chen YC. A review of the dietary flavonoid, kaempferol on human health and cancer chemoprevention. Food Chem. 2013; 138(4):2099-107. [DOI:10.1016/j.foodchem.2012.11.139] [PMID] [PMCID]

[149] Feng H, Cao J, Zhang G, Wang Y. Kaempferol attenuates cardiac hypertrophy via regulation of ASK1/MAPK signaling pathway and oxidative stress. Planta Med. 2017; 83(10):837-45. [DOI:10.1055/s-0043-103415] [PMID]

[150] Yang EJ, Kim GS, Jun M, Song KS. Kaempferol attenuates the glutamate-induced oxidative stress in mouse-derived hippocampal neuronal HT22 cells. Food Funct. 2014; 5(7):1395-402. [DOI:10.1039/c4fo00068d] [PMID]

[151] Yoon JS, Chae MK, Lee SY, Lee EJ. Anti-inflammatory effect of quercetin in a whole orbital tissue culture of Graves' orbitopathy. Br J Ophthalmol. 2012; 96(8):1117-21. [DOI:10.1136/bjophthalmol-2012-301537] [PMID]

[152] Eid HM, Nachar A, Thong F, Sweeney G, Haddad PS. The molecular basis of the antidiabetic action of quercetin in cultured skeletal muscle cells and hepatocytes. Pharmacogn Mag. 2015; 11(41):74-81. [DOI:10.4103/0973-1296.149708] [PMID] [PMCID]

[153] Yang JH, Hsia TC, Kuo HM, Chao PD, Chou CC, Wei YH, et al. Inhibition of lung cancer cell growth by quercetin glucuronides via G2/M arrest and induction of apoptosis. Drug Metab Dispos. 2006; 34(2):296-304. [DOI:10.1124/dmd.105.005280] [PMID]

[154] Tao W, Dong Y, Su Q, Wang H, Chen Y, Xue W, et al. Liquiritigenin reverses depression-like behavior in unpredictable chronic mild stress-induced mice by regulating PI3K/Akt/mTOR mediated BDNF/TrkB pathway. Behav Brain Res. 2016; 308:177-86. [DOI:10.1016/j.bbr.2016.04.039] [PMID]

[155] Liu RT, Tang JT, Zou LB, Fu JY, Lu QJ. Liquiritigenin attenuates the learning and memory deficits in an amyloid protein precursor transgenic mouse model and the underlying mechanisms.Eur J Pharmacol. 2011; 669(1-3):76-83. [DOI:10.1016/j.ejphar.2011.07.051] [PMID]

[156] Scolastici C, Alves de Lima RO, Barbisan LF, Ferreira AL, Ribeiro DA, Salvadori DM. Antigenotoxicity and antimutagenicity of lycopene in HepG2 cell line evaluated by the comet assay and micronucleus test. Toxicol In Vitro. 2008; 22(2):510-4. [DOI:10.1016/j.tiv.2007.11.002] [PMID]

[157] Pirayesh Islamian J, Mehrali H. Lycopene as a carotenoid provides radioprotectant and antioxidant effects by quenching radiation-induced free radical singlet oxygen: An overview. Cell J. 2015; 16(4):386-91. [PMID]

[158] Wang L, Liu S, Pradhan AD, Manson JE, Buring JE, Gaziano JM, et al. Plasma lycopene, other carotenoids, and the risk of type 2 diabetes in women. Am J Epidemiol. 2006; 164(6):576-85. [DOI:10.1093/aje/kwj240] [PMID]

[159] Schagen SK, Zampeli VA, Makrantonaki E, Zouboulis CC. Discovering the link between nutrition and skin aging. Dermatoendocrinol. 2012; 4(3):298-307. [DOI:10.4161/derm.22876] [PMID] [PMCID]

[160] Naguib YM. Antioxidant activities of astaxanthin and related carotenoids. J Agric Food Chem. 2000; 48(4):1150-4. [DOI:10.1021/jf991106k] [PMID]

[161] Lee SJ, Bai SK, Lee KS, Namkoong S, Na HJ, Ha KS, et al. Astaxanthin inhibits nitric oxide production and inflammatory gene expression by suppressing I(kappa)B kinase-dependent NF-kB activation. Mol Cells. 2003; 16(1):97-105. [PMID]

[162] Dong LY, Jin J, Lu G, Kang XL. Astaxanthin attenuates the apoptosis of retinal ganglion cells in db/db mice by inhibition of oxidative stress. Mar Drugs. 2013; 11(3):960-74. [DOI:10.3390/md11030960] [PMID] [PMCID]

[163] Otsuka T, Shimazawa M, Inoue Y, Nakano Y, Ojino K, Izawa H, et al. Astaxanthin protects against retinal damage: Evidence from in vivo and in vitro retinal ischemia and reperfusion models. Curr Eye Res. 2016; 41(11):1465-72. [DOI:10.3109/02713683.2015.1127392] [PMID]

[164] Ignea C, Raadam MH, Motawia MS, Makris AM, Vickers CE, Kampranis SC. Orthogonal monoterpenoid biosynthesis in yeast constructed on an isomeric substrate. Nat Commun. 2019; 10(1):3799. [DOI:10.1038/s41467-019-11290-x] [PMID] [PMCID]

[165] Jiang GZ, Yao MD, Wang Y, Zhou L, Song TQ, Liu H, et al. Manipulation of GES and ERG20 for geraniol overproduction in Saccharomyces cerevisiae. Metab Eng. 2017; 41:57-66. [DOI:10.1016/j.ymben.2017.03.005] [PMID]

[166] Zhang C, Li M, Zhao GR, Lu W. Alpha-Terpineol production from an engineered Saccharomyces cerevisiae cell factory. Microb Cell Fact. 2019; 18(1):160. [DOI:10.1186/s12934-019-1211-0] [PMID] [PMCID]

[167] Paddon CJ, Westfall PJ, Pitera DJ, Benjamin K, Fisher K, McPhee D, et al. High-level semi-synthetic production of the potent antimalarial artemisinin. Nature. 2013; 496(7446):528-32. [DOI:10.1038/nature12051] [PMID]

[168] Wong J, d'Espaux L, Dev I, van der Horst C, Keasling J. De novo synthesis of the sedative valerenic acid in Saccharomyces cerevisiae. Metab Eng. 2018; 47:94-101. [DOI:10.1016/j.ymben.2018.03.005] [PMID]

[169] Ma B, Liu M, Li ZH, Tao X, Wei DZ, Wang FQ. Significantly enhanced production of patchoulol in metabolically engineered Saccharomyces cerevisiae. J Agric Food Chem. 2019; 67(31):8590-8. [DOI:10.1021/acs.jafc.9b03456] [PMID]

[170] Ignea C, Trikka FA, Nikolaidis AK, Georgantea P, Ioannou E, Loupassaki S, et al. Efficient diterpene production in yeast by engineering Erg20p into a geranylgeranyl diphosphate synthase. Metab Eng. 2015; 27:65-75. [DOI:10.1016/j.ymben.2014.10.008] [PMID]

[171] Chen J, Fan F, Qu G, Tang J, Xi Y, Bi C, et al. Identification of Absidia orchidis steroid 11β-hydroxylation system and its application in engineering Saccharomyces cerevisiae for one-step biotransformation to produce hydrocortisone. Metab Eng. 2020; 57:31-42. [DOI:10.1016/j.ymben.2019.10.006] [PMID]

[172] Scheler U, Brandt W, Porzel A, Rothe K, Manzano D, Božić D, et al. Elucidation of the biosynthesis of carnosic acid and its reconstitution in yeast. Nat Commun. 2016; 7:12942. [DOI:10.1038/ncomms12942] [PMID] [PMCID]

[173] Wang P, Wei W, Ye W, Li X, Zhao W, Yang C, et al. Synthesizing ginsenoside Rh2 in Saccharomyces cerevisiae cell factory at high-efficiency. Cell Discov. 2019; 5:5. [DOI:10.1038/s41421-018-0075-5] [PMID] [PMCID]

[174] Wang P, Wei Y, Fan Y, Liu Q, Wei W, Yang C, et al. Production of bioactive ginsenosides Rh2 and Rg3 by metabolically engineered yeasts. etab Eng. 2015; ;29:97-105. [DOI:10.1016/j.ymben.2015.03.003] [PMID]

[175] Zhu M, Wang C, Sun W, Zhou A, Wang Y, Zhang G, et al. Boosting 11-oxo-β-amyrin and glycyrrhetinic acid synthesis in Saccharomyces cerevisiae via pairing novel oxidation and reduction system from legume plants. Metab Eng. 2018; 45:43-50. [DOI:10.1016/j.ymben.2017.11.009] [PMID]

[176] Brower V. Nutraceuticals: Poised for a healthy slice of the healthcare market? Nat Biotechnol. 1998; 16(8):728-31. [DOI:10.1038/nbt0898-728] [PMID]

[177] Ping Y, Li X, You W, Li G, Yang M, Wei W, et al. De novo production of the plant-derived tropine and pseudotropine in yeast. ACS Synth Biol. 2019; 8(6):1257-62. [DOI:10.1021/acssynbio.9b00152] [PMID]

[178] Shrivastava A, Pal M, Sharma RK. Pichia as yeast cell factory for production of industrially important bio-products: Current trends, challenges, and future prospects. J. Bioresour. Bioprod. 2023; 18(2):108-24. [DOI:10.1016/j.jobab.2023.01.007]

[179] Wang TY, Tsai YH, Yu IZ, Chang TS. Improving 3′-hydroxygenistein production in recombinant Pichia pastoris using periodic hydrogen peroxide-shocking strategy. J Microbiol Biotechnol. 2016; 26(3):498-502. [DOI:10.4014/jmb.1509.09013] [PMID]

[180] Wriessnegger T, Augustin P, Engleder M, Leitner E, Müller M, Kaluzna I, et al. Production of the sesquiterpenoid (+)-nootkatone by metabolic engineering of Pichia pastoris. Metab Eng. 2014; 24:18-29. [DOI:10.1016/j.ymben.2014.04.001] [PMID]

[181] Moser S, Strohmeier GA, Leitner E, Plocek TJ, Vanhessche K, Pichler H. Whole-cell (+)-ambrein production in the yeast Pichia pastoris. Metab Eng Commun. 2018; 7:e00077. [DOI:10.1016/j.mec.2018.e00077] [PMID] [PMCID]

[182] Zhang X, Wang D, Duan Y, Zheng X, Lin Y, Liang S. Production of lycopene by metabolically engineered Pichia pastoris. Biosci Biotechnol Biochem. 2020; 84(3):463-70. [DOI:10.1080/09168451.2019.1693250] [PMID]

[183] Schaefer S, Piontek M, Ahn SJ, Papendieck A, Janowicz ZA, Timmermans I, et al. Recombinant hepatitis B vaccines-disease characterization and vaccine production. In: Gellissen G, editor. Hansenula polymorpha: Biology and applications. New Jersey: Wiley; 2002. [DOI:10.1002/3527602356.ch12]

[184] Champion CR. Heplisav-B: A hepatitis B vaccine with a novel adjuvant. Ann Pharmacother. 2021; 55(6):783-91. [DOI:10.1177/1060028020962050] [PMID]

[185] Gellissen G, Kunze G, Gaillardin C, Cregg JM, Berardi E, Veenhuis M, et al. New yeast expression platforms based on methylotrophic Hansenula polymorpha and Pichia pastoris and on dimorphic Arxula adeninivorans and Yarrowia lipolytica-a comparison. FEMS Yeast Res. 2005; 5(11):1079-96. [DOI:10.1016/j.femsyr.2005.06.004] [PMID]

[186] Madzak C, Gaillardin C, Beckerich JM. Heterologous protein expression and secretion in the non-conventional yeast Yarrowia lipolytica: A review. J Biotechnol. 2004; 109(1-2):63-81. [DOI:10.1016/j.jbiotec.2003.10.027] [PMID]

[187] James LC, Strick CA. Multiple integrative vectors and Yarrowia lipolytica transformants. Washington, D.C.: U.S. Government Publishing Office: 1998. [Link]

[188] Hamsa PV, Chattoo BB. Cloning and growth-regulated expression of the gene encoding the Hepatitis B virus middle surface antigen in Yarrowia lipolytica. Gene. 1994; 143(2):165-70. [DOI:10.1016/0378-1119(94)90092-2] [PMID]

[189] Hardwicke J, Schmaljohann D, Boyce D, Thomas D. Epidermal growth factor therapy and wound healing-past, present and future perspectives. Surgeon. 2008; 6(3):172-7. [DOI:10.1016/S1479-666X(08)80114-X] [PMID]

[190] Gasmi N, Ayed A, Nicaud JM, Kallel H. Design of an efficient medium for heterologous protein production in Yarrowia lipolytica: Case of human interferon alpha 2b. Microb Cell Fact. 2011; 10:38. [PMID]

[191] Gasmi N, Ayed A, Ammar BB, Zrigui R, Nicaud JM, Kallel H. Development of a cultivation process for the enhancement of human interferon alpha 2b production in the oleaginous yeast, Yarrowia lipolytica. Microb Cell Fact. 2011; 10:90. [PMID] [PMCID]

[192] Gull I, Samra ZQ, Aslam MS, Athar MA. Heterologous expression, immunochemical and computational analysis of recombinant human interferon alpha 2b. Springerplus. 2013; 2(1):264. [DOI:10.1186/2193-1801-2-264] [PMID] [PMCID]

[193] Davidow LS, DeZeeuw JR, Franke AE. Expression and secretion of heterologous proteins by Yarrowia lipolytica transformants. Washington, D.C.: U.S. Government Publishing Office; 1990. [Link]

[194] Klos A, Tenner AJ, Johswich KO, Ager RR, Reis ES, Köhl J. The role of the anaphylatoxins in health and disease. Mol Immunol. 2009; 46(14):2753-66. [DOI:10.1016/j.molimm.2009.04.027] [PMID] [PMCID]

[195] Tharaud C, Ribet AM, Costes C, Gaillardin C. Secretion of human blood coagulation factor XIIIa by the yeast Yarrowia lipolytica. Gene. 1992; 121(1):111-9. [DOI:10.1016/0378-1119(92)90168-O] [PMID]

[196] Gemmati D, Vigliano M, Burini F, Mari R, El Mohsein HH, Parmeggiani F, et al. Coagulation factor XIIIA (F13A1): Novel perspectives in treatment and pharmacogenetics. Curr Pharm Des. 2016; 22(11):1449-59. [DOI:10.2174/1381612822666151210122954] [PMID]

[197] Swennen D, Paul MF, Vernis L, Beckerich JM, Fournier A, Gaillardin C. Secretion of active anti-Ras single-chain Fv antibody by the yeasts Yarrowia lipolytica and Kluyveromyces lactis. Microbiology. 2002; 148(1):41-50. [DOI:10.1099/00221287-148-1-41] [PMID]

[198] Coulon S, Mappus E, Cuilleron C, Baty D. Improving the specificity of an anti-estradiol antibody by random mutagenesis and phage display. Dis Markers. 2000; 16(1-2):33-5. [DOI:10.1155/2000/978512] [PMID] [PMCID]

[199] Dudich E. MM-093, a recombinant human alpha-fetoprotein for the potential treatment of rheumatoid arthritis and other autoimmune diseases. Curr Opin Mol Ther. 2007; 9(6):603-10. [PMID]

[200] Palmer CM, Miller KK, Nguyen A, Alper HS. Engineering 4-coumaroyl-CoA derived polyketide production in Yarrowia lipolytica through a β-oxidation mediated strategy. Metab Eng. 2020; 57:174-81. [DOI:10.1016/j.ymben.2019.11.006] [PMID]

[201] Lv Y, Marsafari M, Koffas M, Zhou J, Xu P. Optimizing oleaginous yeast cell factories for flavonoids and hydroxylated flavonoids biosynthesis. ACS Synth Biol. 2019; 8(11):2514-23. [DOI:10.1021/acssynbio.9b00193] [PMID]

[202] Olesen M, Gudmand-Høyer E. Efficacy, safety, and tolerability of fructooligosaccharides in the treatment of irritable bowel syndrome. Am J Clin Nutr. 2000; 72(6):1570-5. [DOI:10.1093/ajcn/72.6.1570] [PMID]

[203] Kumar CG, Sripada S, Poornachandra Y. Status and future prospects of fructooligosaccharides as nutraceuticals. In: Grumezescu AM, Holban AM, editor. Role of materials science in food bioengineering. Amsterdam: Elsevier; 2018. [DOI:10.1016/B978-0-12-811448-3.00014-0]

[204] Kapoor R, Huang YS. Gamma linolenic acid: An antiinflammatory omega-6 fatty acid. Curr Pharm Biotechnol. 2006; 7(6):531-4. [DOI:10.2174/138920106779116874] [PMID]

[205] Brinton EA, Mason RP. Prescription omega-3 fatty acid products containing highly purified eicosapentaenoic acid (EPA). Lipids Health Dis. 2017; 16(1):23. [DOI:10.1186/s12944-017-0415-8] [PMID] [PMCID]

[206] Liu HH, Madzak C, Sun ML, Ren LJ, Song P, Huang H, et al. Engineering Yarrowia lipolytica for arachidonic acid production through rapid assembly of metabolic pathway. Biochem Eng J. 2017; 119:52-8. [DOI:10.1016/j.bej.2016.12.004]

[207] Tallima H, El Ridi R. Arachidonic acid: Physiological roles and potential health benefits-a review. J Adv Res. 2018; 11:33-41. [DOI:10.1016/j.jare.2017.11.004] [PMID] [PMCID]

[208] Bailey RB, Trueheart J, Madden KT, inventors; DSM IP Assets BV, assignee. Production of sterols in oleaginous yeast and fungi. Washington, D.C.: U.S. Government Publishing Office; 2013. [Link]

[209] Cofán M, Ros E. Clinical application of plant sterol and stanol products. J AOAC Int. 2015; 98(3):701-6. [DOI:10.5740/jaoacint.SGECofan] [PMID]

[210] Sharpe PL Rick WY, Zhu QQ. Washington, D.C.: U.S. Government Publishing Office; 2014. [Link]

[211] Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. Mol Aspects Med. 2005; 26(6):459-516. [DOI:10.1016/j.mam.2005.10.001] [PMID]

[212] Porro D, Sauer M, Branduardi P, Mattanovich D. Recombinant protein production in yeasts. Mol Biotechnol. 2005; 31:245-59. [DOI:10.1385/MB:31:3:245]

[213] Jia D, Xu S, Sun J, Zhang C, Li D, Lu W. Yarrowia lipolytica construction for heterologous synthesis of α-santalene and fermentation optimization. Appl Microbiol Biotechnol. 2019; 103(8):3511-20. [DOI:10.1007/s00253-019-09735-w] [PMID]

[214] Cao X, Lv YB, Chen J, Imanaka T, Wei LJ, Hua Q. Metabolic engineering of oleaginous yeast Yarrowia lipolytica for limonene overproduction. Biotechnol Biofuels. 2016; 9:214. [DOI:10.1186/s13068-016-0626-7] [PMID] [PMCID]

[215] Guo X, Sun J, Li D, Lu W. Heterologous biosynthesis of (+)-nootkatone in unconventional yeast Yarrowia lipolytica. Biochem Eng J. 2018; 137:125-31. [DOI:10.1016/j.bej.2018.05.023]

[216] Wu Y, Xu S, Gao X, Li M, Li D, Lu W. Enhanced protopanaxadiol production from xylose by engineered Yarrowia

lipolytica. Microb Cell Fact. 2019; 18(1):83. [DOI:10.1186/s12934-019-1136-7] [PMID] [PMCID]

[217] Du HX, Xiao WH, Wang Y, Zhou X, Zhang Y, Liu D, et al. Engineering Yarrowia lipolytica for campesterol overproduction. PLoS One. 2016; 11(1):e0146773. [DOI:10.1371/journal.pone.0146773] [PMID] [PMCID]

[218] Li D, Wu Y, Zhang C, Sun J, Zhou Z, Lu W. Production of triterpene ginsenoside compound K in the non-conventional yeast Yarrowia lipolytica. J Agric Food Chem. 2019; 67(9):2581-8. [DOI:10.1021/acs.jafc.9b00009] [PMID]

[219] Tramontin LRR, Kildegaard KR, Sudarsan S, Borodina I. Enhancement of astaxanthin biosynthesis in oleaginous yeast Yarrowia lipolytica via microalgal pathway. Microorganisms. 2019; 7(10):472. [DOI:10.3390/microorganisms7100472] [PMID] [PMCID]

[220] Janek T, Dobrowolski A, Biegalska A, Mirończuk AM. Characterization of erythrose reductase from Yarrowia lipolytica and its influence on erythritol synthesis. Microb Cell Fact. 2017; 16(1):118. [DOI:10.1186/s12934-017-0733-6] [PMID] [PMCID]

[221] Rymowicz W, Rywińska A, Marcinkiewicz M. High-yield production of erythritol from raw glycerol in fed-batch cultures of Yarrowia lipolytica. Biotechnol Lett. 2009; 31(3):377-80. [DOI:10.1007/s10529-008-9884-1] [PMID]

[222] Yang LB, Zhan XB, Zheng ZY, Wu JR, Gao MJ, Lin CC. A novel osmotic pressure control fed-batch fermentation strategy for improvement of erythritol production by Yarrowia lipolytica from glycerol. Bioresour Technol. 2014; 151:120-7. [DOI:10.1016/j.biortech.2013.10.031] [PMID]

[223] Mirończuk AM, Rakicka M, Biegalska A, Rymowicz W, Dobrowolski A. A two-stage fermentation process of erythritol production by yeast Y. lipolytica from molasses and glycerol. Bioresour Technol. 2015; 198:445-55. [DOI:10.1016/j.biortech.2015.09.008] [PMID]

[224] Carly F, Vandermies M, Telek S, Steels S, Thomas S, Nicaud J-M, et al. Enhancing erythritol productivity in Yarrowia lipolytica using metabolic engineering. Metab Eng. 2017; 42:19-24. [DOI:10.1016/j.ymben.2017.05.002] [PMID]

[225] Tomaszewska L, Rywińska A, Rymowicz W. High selectivity of erythritol production from glycerol by Yarrowia lipolytica. Biomass Bioenergy. 2014; 64:309-20. [DOI:10.1016/j.biombioe.2014.03.005]

[226] Ghezelbash GR, Nahvi I, Emamzadeh R. Improvement of erythrose reductase activity, deletion of by-products and statistical media optimization for enhanced erythritol production from Yarrowia lipolytica mutant 49. Curr Microbiol. 2014; 69(2):149-57. [DOI:10.1007/s00284-014-0562-3] [PMID]

[227] Rywińska A, Marcinkiewicz M, Cibis E, Rymowicz W. Optimization of medium composition for erythritol production from glycerol by Yarrowia lipolytica using response surface methodology. Prep Biochem Biotechnol. 2015; 45(6):515-29. [DOI:10.1080/10826068.2014.940966] [PMID]

[228] Livesey G. Health potential of polyols as sugar replacers, with emphasis on low glycaemic properties. Nutr Res Rev. 2003; 16(2):163-91. [DOI:10.1079/NRR200371] [PMID]

[229] André A, Chatzifragkou A, Diamantopoulou P, Sarris D, Philippoussis A, Galiotou-Panayotou M, et al. Biotechnological conversions of bio-diesel-derived crude glycerol by Yarrowia lipolytica strains. Eng Life Sci. 2009; 9(6):468-78. [DOI:10.1002/elsc.200900063]

[230] Chatzifragkou A, Makri A, Belka A, Bellou S, Mavrou M, Mastoridou M, et al. Biotechnological conversions of biodiesel derived waste glycerol by yeast and fungal species. Energy. 2011; 36(2):1097-108. [DOI:10.1016/j.energy.2010.11.040]

[231] Chatzifragkou A, Petrou I, Gardeli C, Komaitis M, Papanikolaou S. Effect of Origanum vulgare L. essential oil on growth and lipid profile of Yarrowia lipolytica cultivated on glycerol-based media. J Am Oil Chem Soc. 2011; 88(12):1955-64. [DOI:10.1007/s11746-011-1870-4]

[232] Rymowicz W, Fatykhova AR, Kamzolova SV, Rywińska A, Morgunov IG. Citric acid production from glycerol-containing waste of biodiesel industry by Yarrowia lipolytica in batch, repeated batch, and cell recycle regimes. Appl Microbiol Biotechnol. 2010; 87(3):971-9. [DOI:10.1007/s00253-010-2561-z] [PMID]

[233] Mirończuk AM, Furgała J, Rakicka M, Rymowicz W. Enhanced production of erythritol by Yarrowia lipolytica on glycerol in repeated batch cultures. J Ind Microbiol Biotechnol. 2014; 41(1):57-64. [DOI:10.1007/s10295-013-1380-5] [PMID] [PMCID]

[234] Rywińska A, Rymowicz W, Żarowska B, Wojtatowicz M. Biosynthesis of citric acid from glycerol by acetate mutants of Yarrowia lipolytica in fed-batch fermentation. Food Technol Biotechnol. 2009; 47(1):1-6. [Link]

[235] Tomaszewska L, Rywińska A, Gładkowski W. Production of erythritol and mannitol by Yarrowia lipolytica yeast in media containing glycerol.J Ind Microbiol Biotechnol. 2012; 39(9):1333-43. [DOI:10.1007/s10295-012-1145-6] [PMID] [PMCID]

[236] Godswill AC. Sugar alcohols: Chemistry, production, health concerns and nutritional importance of mannitol, sorbitol, xylitol, and erythritol. Int J Adv Acad Res. 2017; 3(2):31-66. [Link]

[237] RywiŁ A, Tomaszewska L, Rymowicz W. Erythritol biosynthesis by Yarrowia lipolytica yeast under various culture conditions. Afr J Microbiol Res. 2013; 7(27):3511-6. [Link]