

A Comparative Review of Plant and Microbial Antioxidant Secondary Metabolites

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Abstract

Background and Objective: Disturbance of reactive species produced through various physiological and biochemical processes causes damages to the cells, leading to cell apoptosis. In addition to medical importance, compounds with antioxidant activity can prevent radical species linked damages in food industries. Antioxidants can be described as valuable food preservatives, which promote food nutritional values via preventing oxidation of various diverse contents, majorly lipids, in addition to food deterioration. Due to the high costs and dangerous effects on human health reported for synthetic antioxidants, the search for natural antioxidant compounds has increased. Therefore, the objective of the present review was to overview natural antioxidants from plants and microorganisms as well as their diversity and industrial uses.

Results and Conclusion: Plants and microorganisms are significant natural sources of diverse antioxidants. Nevertheless, the vast diversity of microorganisms and their metabolites as well as their easier manipulations highlight the environmental-friendly antioxidant production techniques from microorganisms that must be revised, compared to plants or synthetic antioxidants. Phenolics and terpenoids are the dominant antioxidants produced in plants, while the microbial antioxidants vary, including carotenoids, polyketides and polysaccharides. This review clearly highlights the competency of microbial bioactive metabolites as the alternative sources of bioactive antioxidants for future of food industries. Elucidating structural and physicochemical characteristics of microbial antioxidants enables the discovery of emerging antioxidants and their mechanisms of action, leading to the disclosure of various strategies in the industries.

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1. Introduction

The reactive species of oxygen, nitrogen and sulfur, possess an unstable unpaired electron in their atomic orbital, behaving as an oxidizing or reducing agent [1]. Accumulation of these reactive species in the body causes oxidative stress, which is harmful to vital biomolecules (lipids, carbohydrates, proteins and nucleic acids). Furthermore, it leads to the development of life-threatening disorders,

including chronic and degenerative diseases majorly cancers and neurodegenerative diseases [2]. To prevent oxidative-related disorders, a balance should be created between production and degradation of reactive species. First, endogenous antioxidants, including enzymatic and non-enzymatic antioxidant agents, ameliorate this unbalanced status via maintaining detrimental reactive species at a

nontoxic concentration. However in most conditions, it is needed that endogenous defense is augmented by consuming exogenous antioxidants to overcome overproduction of ROS due to endogenous or exogenous stimuli [3]. Antioxidants can suppress oxidation of other substances by removing free radicals or interrupting their chain reaction, decomposing hydroperoxides and chelating prooxidative metal ions. Based on their molecular weight, mechanisms of action and water and lipid solubilities, antioxidants can be grouped into enzymatic or non-enzymatic antioxidants (Figure 1) [4]. Compounds with antioxidant activity can prevent radical species-related damages including health and economic damages and food deterioration. Therefore, antioxidants can be addressed as valuable food preservatives, which promote food nutritional values via preventing oxidation of various lipid-soluble vitamins, carotenes and essential fatty acids as well as delaying food deterioration [3,5]. Due to the high costs, toxicity and dangerous effects on human health reported from synthetic antioxidants, including hydroxyl-anisole, butylated hydroxytoluene and propyl gallate, search for natural antioxidant compounds has increased [6]. This review provides an overview of natural antioxidants from plants and microorganisms. Industrial use of these antioxidants are discussed as well. Future directions of naturally occurring antioxidants can be concluded from this comparative overview.

1.1 Plant-derived antioxidants

A majority of natural antioxidants are derived from plants (fruits, vegetables, herbs and spices) (Figure 2), mainly rich in phenolics, vitamins and carotenoids [7]. Families of plants such as *Ericaceae*, *Rosaceae*, *Juglandaceae* and *Empetraceae* [8] highly include antioxidant compounds. Essential oils of spices and herbs [9] and aqueous tea extracts containing various flavonoids [10] have been demonstrated as excellent natural antioxidant sources. In addition, processing byproducts of fruit and legume such as apple, olive and grape pomace [11,12], are rich in anthocyanins, catechins, flavanols and phenolic acids with high content of lycopene and other carotenoids [13] can be natural sources of antioxidants. Based on previous reports, biocompounds, including phenolics, flavonoids, carotenoids, sterols, glucosinolates and other sulphur-containing compounds isolated from plants, exhibited potential bioactivities and can be utilized as antimicrobial and antioxidant additives in food industries [14,15].

Use of bioactive molecules in food, cosmetic and pharmaceutical industries has recently increased as safe alternatives for synthetic antioxidative products, which are known for their carcinogenic effects [16]. Interestingly, plant-derived antioxidants show a better antioxidant activity than the synthetic antioxidants [17]. Plant-derived antioxidants have comprehensively been studied by Amarowicz et al. and Atasoy et al. [18,19].

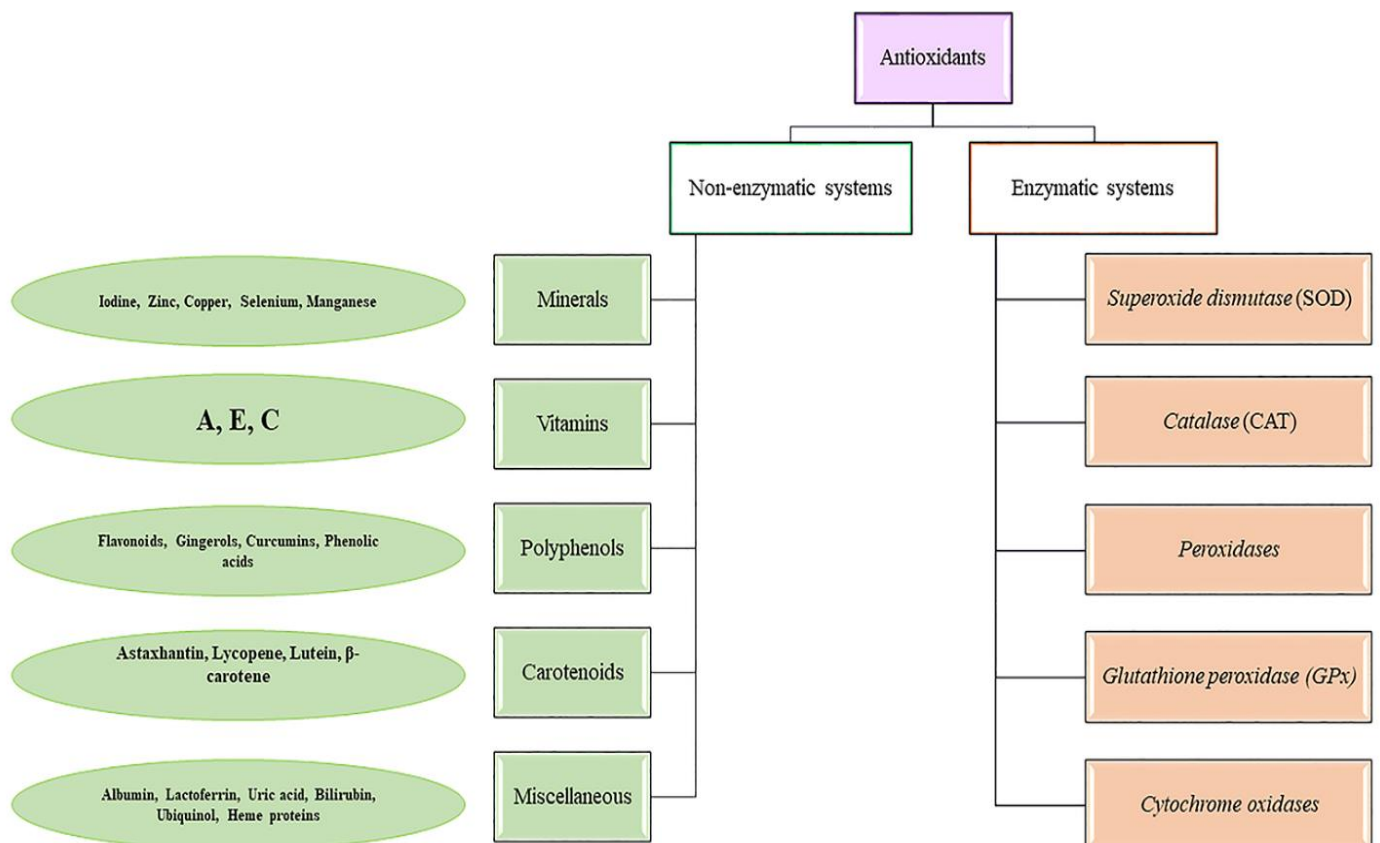
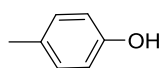
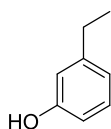


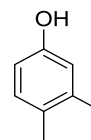
Figure 1. General classification of the antioxidant agents



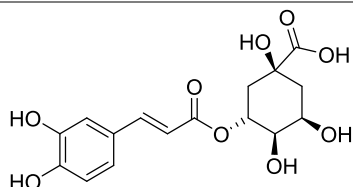
p-cresol



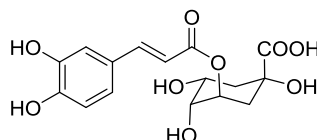
3-ethylphenol



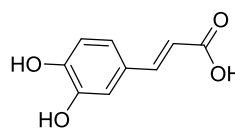
3,4-dimethylphenol



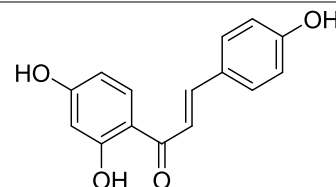
Chlorogenic acid



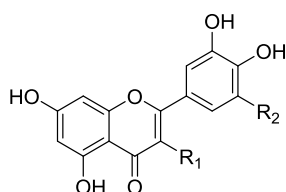
5-Caffeoylquinic acid (5-CQA)



Caffeic acid



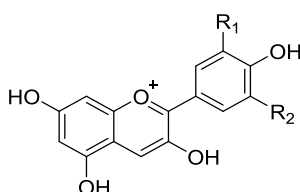
Isoliquiritigenin (256.25 g/mol)



Flavonoids

R₁

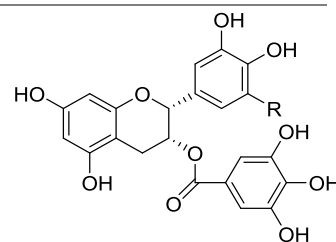
R₂



Anthocyanidin

R₁

R₂



(-)-Epigallocatechingallate

Luteolin

H

H

Pelargonidin

H

H

Quercetin

OH

H

Cyanidin

OH

H

(EGCG): R = OH

MyricetinOH

OH

Peonidin

OCH₃

H

(-)-Epicatechingallate (ECG):

Quercitrin

O-rhamnose

H

Delphinidin

OH

OH

= H

Isoquercitrin

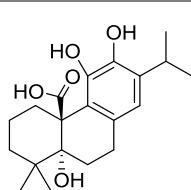
O-glucose

H

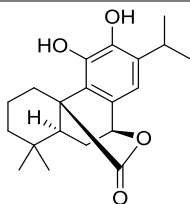
Petunidin

OCH₃

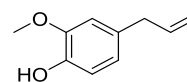
OH



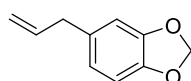
Carnosic acid



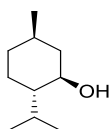
Carnosol



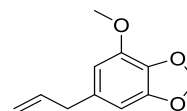
Eugenol



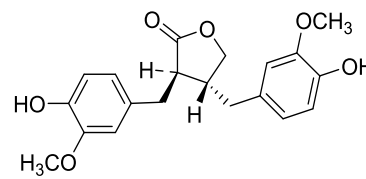
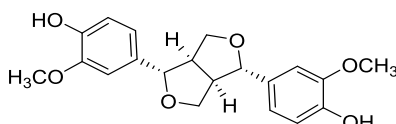
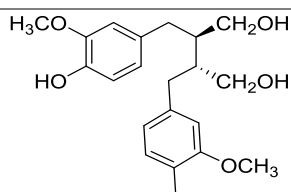
Safrole



Menthol



Myristicin



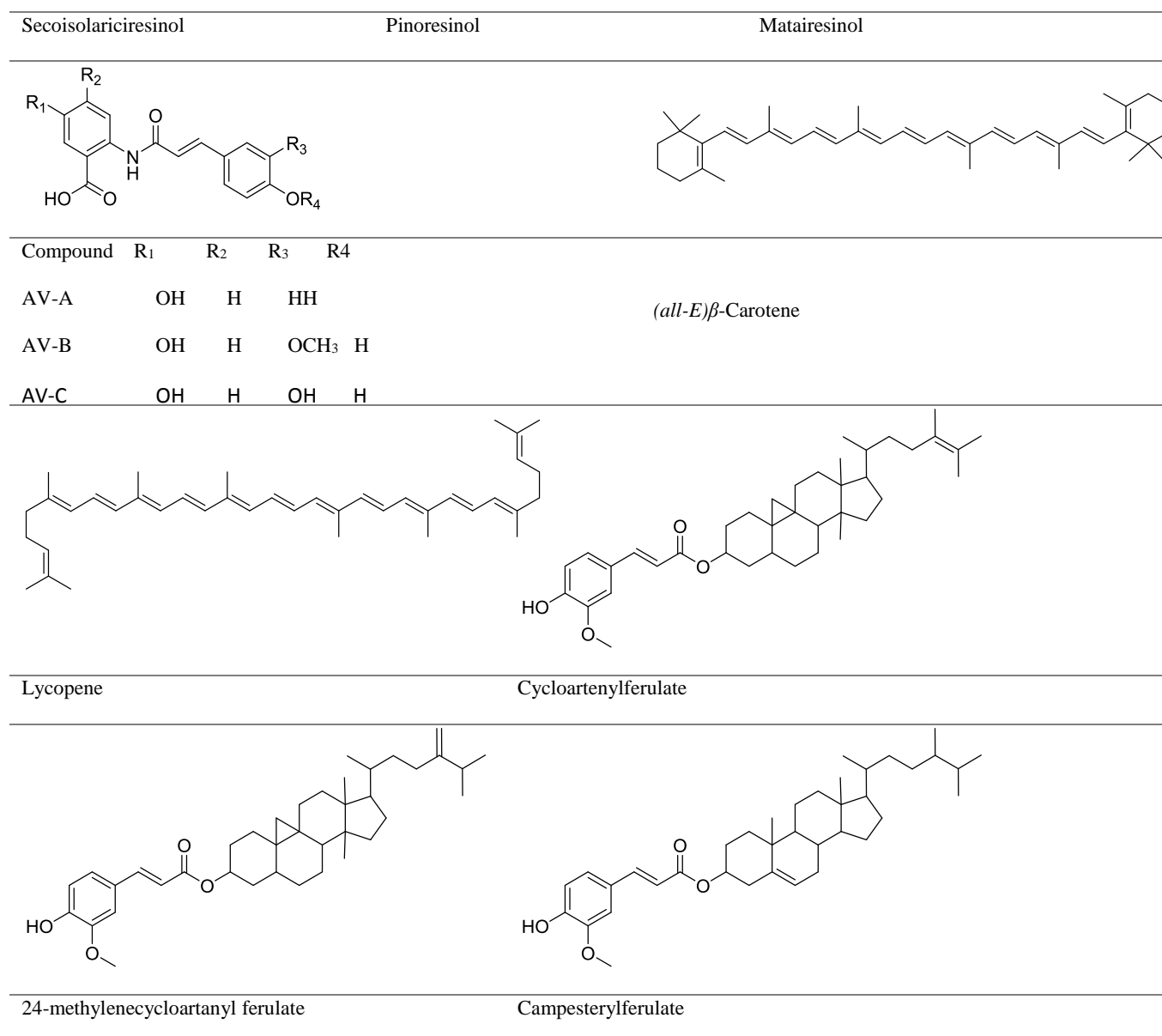


Figure 2. Structures of the major groups of plant-derived antioxidants

1.2. Algae (micro and macro)-derived antioxidants

Extreme environmental conditions of algae induce various oxidative reagents in these photosynthetic living cells. These microorganisms as widely available aquatic plants produce natural antioxidative compounds for protecting themselves against oxidation. Micro and macroalgae, especially species belonging to *Chlorella*, *Dunaliella*, *Scenedesmus* and *Haematococcus* genera, can be considered as a rich source of potent antioxidants [20]. The algal antioxidants play critical roles against various cancers, neurological diseases and aging [21,22]. It has been demonstrated that the green, red and brown algae as well as cyanobacteria include high radical scavenging activities [20,23]. Vitamins E and C, α and β carotenoids, zeaxanthin, chlorophylls and polyphenols are the major antioxidants found in algae [24]. Positive correlations between the antioxidant activity and phenolic content have been demonstrated for cyanobacteria and

microalgae [25]. Algal antioxidants have been shown in Table 1.

1.3 Microbial-derived antioxidants

Microorganisms, especially Actinobacteria, are rich sources of natural compounds with extensive medical, nutritional, agricultural and industrial uses [26-28]. Several compounds with various chemical structures and significant antioxidant activities have been isolated from microbial sources [29] and depicted in Figure 3. In addition, various bacterial and fungal metabolites with antioxidant and other biological activities have been reported (Tables 2 and 3).

1.3.1. Microbial carotenoids

Although chemical synthesis of carotenoids or their extraction from plants has been limited due to low yields, high production costs and environmental contamination, the needs for carotenoids in various industries has increased.

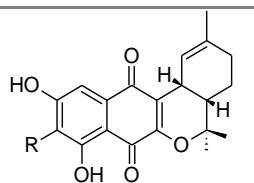
Table 1 Biological activities identified from algal-derived antioxidant metabolites

Antioxidant compounds (g mol ⁻¹)	Chemical Category	Antioxidant activity	Algal sources	Reference
B-Carotene 536.8726 Fucoxanthin 658.91 Lutein 568.871 Xanthophylls 568.886 Zeaxanthin 568.88 Astaxanthin	Carotenoids	Fucoxanthin can scavenge free radicals and effectively inhibit the formation of intracellular ROS, DNA damage, and apoptosis induced by H ₂ O ₂ . Lutein intake elevates endogenous antioxidant expressions. It significantly suppresses malondialdehyde production. Its oral administration significantly recovers the glutathione and vitamin C levels in the eyes of the LPS-treated mice. Xanthophylls possess the ability to act as chain-breaking antioxidants in the peroxidation of membranous. Phospholipids	<i>Chondrus crispus</i> <i>Mastocarpus stellatus</i> Brown and red algae <i>Haematococcus pluvialis</i>	[61-70]
Terpenoids Styodiol 412.614 Isoepitaonidiol 412.614 Taondiol 412.614	Phenolic Compound	They quench singlet oxygen and hydrogen transfer	<i>Taonia atomaria</i> <i>Cystoseria</i> sp.	[71,72]
Phycocerythrin (250,000 Daltons) Phycocyanin 18400 - 30000	Phycobilin pigments	Phycocerythrin alleviates the effect of H ₂ O ₂ , scavenges extra-electron due to plenty of double-bond. Phycocyanin scavenges alkoxyl, hydroxyl & peroxy radicals, inhibits microsomal lipid peroxidation & reduces carbon tetrachloride-induced lipid peroxidation <i>in vivo</i>	Red algae in general	[73-76]
Catechin 290.26 Epicatechin 290.26 Gallate 442.37 Flavonoids Phlorotannins	Catechin	Exhibit DPPH scavenging activity	<i>Halimeda</i> sp. <i>Palmaria palmata</i> <i>Sargassum pallidum</i> <i>Fucus vesiculosus</i>	[77]
Fucoidan 658.9063 Alginate 398.317 Laminarin 504.438 Sulfatedgalactans Sulfated Glycosaminoglycan	Sulphated poly saccharides	Exhibits inhibitory effect on MMP-9 and DPPH and hydroxyl radical scavenging activity. It blocks hydroxyl radical induced DNA oxidation. Exhibits antioxidant activity due to its molecular structure, degree, and length of branching and the monosaccharide constituents. Exhibits antioxidant activity due to the high content of sulfate group. Successfully reduces ALT and AST and lipid peroxidation	<i>Turbinaria conoides</i> <i>Laminaria japonica</i> Most red algae Some marine red algae <i>Sargassum wightii</i> <i>Porphyra</i> sp.	[78-82]
Ascorbate 198.11 Vitamin A 286.4516	Vitamins	Vitamin C, changes to the ascorbate radical by donating an electron to the lipid radical in order to terminate the lipid peroxidation chain reaction. The antioxidant activity of vitamin A is conferred by the hydrophobic chain of polyene units that can quench singlet oxygen and stabilize peroxy radicals	<i>Chondrus crispus</i> <i>Mastocarpus stellatus</i> <i>Sargassum</i> sp. <i>Kappaphycus alvarezii</i>	[83,84]

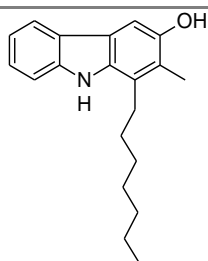
Therefore, introduction of appropriate alternative sources is vital [30]. All types of microorganisms, including bacteria, fungi, yeast and microalgae, can be considered as a source of carotenoid production from low-cost substrates. A number of microorganisms, including *Sporobolomyces roseus*, and *S. patagonicus*, are introduced as producers of an extensive range of carotenoids such as γ and β -carotene (536.8726 g mol⁻¹), torulene (534.86 g mol⁻¹), lycopene (536.873 g mol⁻¹) and astaxanthin (596.841 g mol⁻¹) [31]. Novel and cost-effective C50 carotenoids can be produced via microorganisms using agricultural byproducts [32].

1.3.2. Microbial phenolic compounds

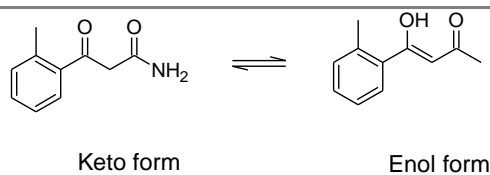
Although phenolic compounds are considered common types of antioxidants in plants, gallic acid, protocatechuic acid and ellagic acid are microbial-derived phenolic compounds, which demonstrate potential antioxidant activities due to their function as reducing agents, hydrogen donors and singlet oxygen quenchers [29,33].



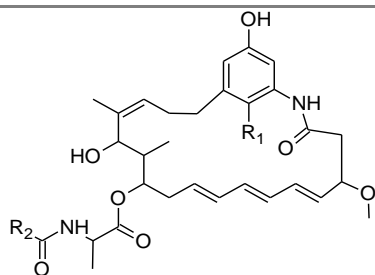
Naphterpin R=CH₃
7-demethylnaphterpin R=H



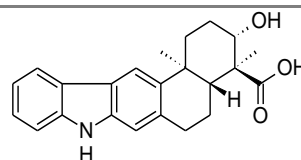
Carazostatin
(1-heptyl-3-hydroxy-2-methyl carbazole)



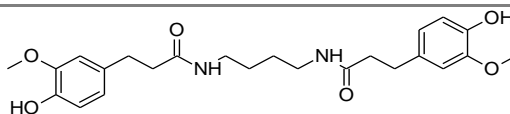
3-(2-methylphenyl) propionamide 3-one



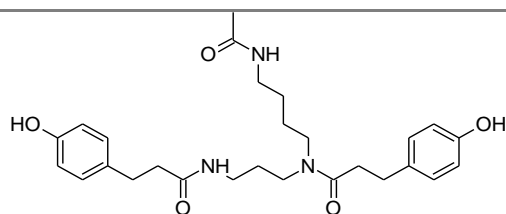
Mycotrienin II R₁ OH
R₂ OH
Trienomycin A H
Trienomycin B H CH₂CH(CH₃)₂



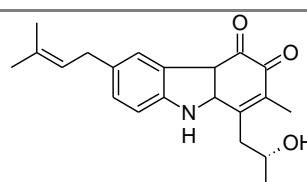
Xiamycin A



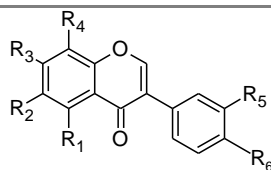
JBIR-94



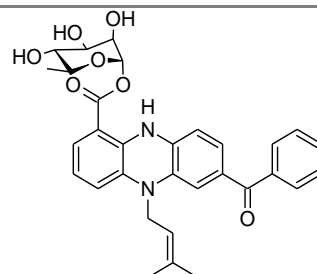
JBIR-125



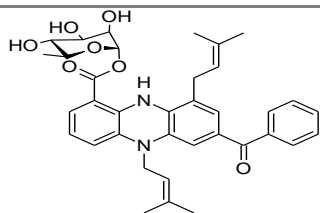
Carquinostatin



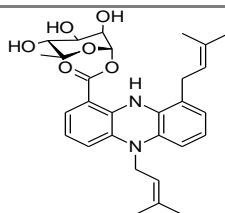
3, 4, 7-trihydroxyisoflavone R₁=R₂=H R₃=R₄ R₅=H
R₆=OH
4, 7, 8-trihydroxyflavone R₁=R₂=H R₃=OH R₄=OH
R₅=R₆=OH
4,7,8-trihydroxyisoflavone R₁=OH R₂=H R₃=OH
R₄=Cl R₅=R₆=OH



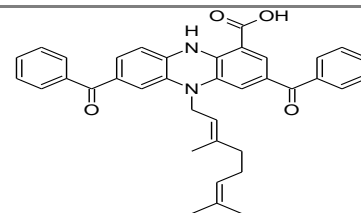
Aestivophoenins A



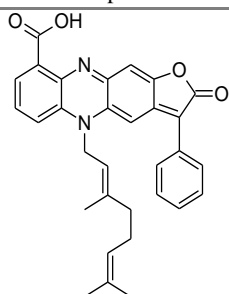
Aestivophoenin B



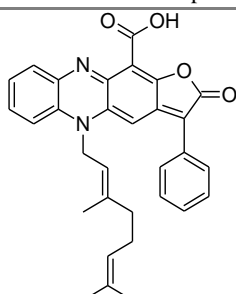
Aestivophoenin C



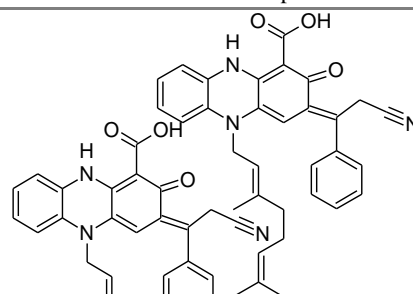
Benthophoenin



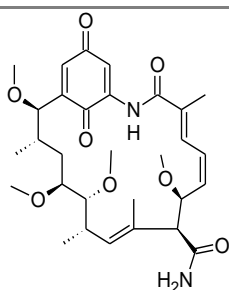
Benthocyanin A



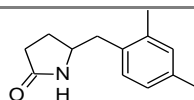
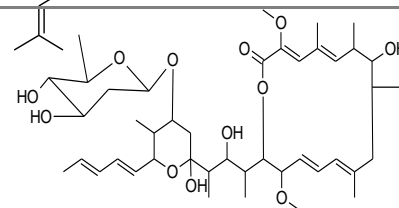
Benthocyanin B



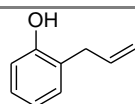
Benthocyanin C



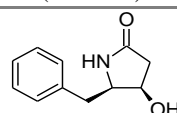
Dihydroherbimycin

5-(2,4-dimethylbenzyl)pyrrolidin-2-on
(DMBPO)

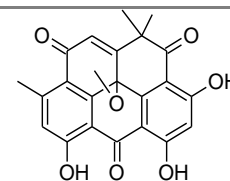
Compound PC-766 B



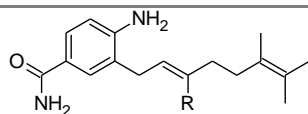
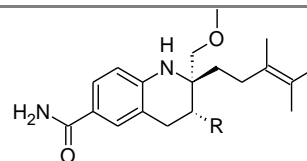
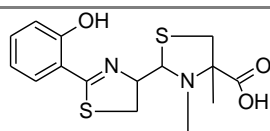
2-allyloxyphenol



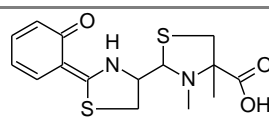
Streptopyrrolidine



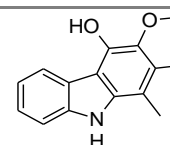
Resistoflavin methyl ether

Benzastatin A R=CH₂OMe
Benzastatin B R=CH₃Benzastatin C R=Cl
Benzastatin D R=OH

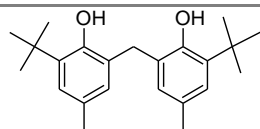
Thiazostatin A



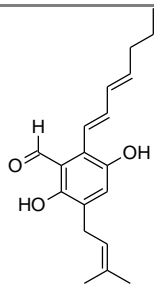
Thiazostatin B



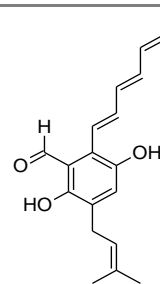
Carbazomycin B



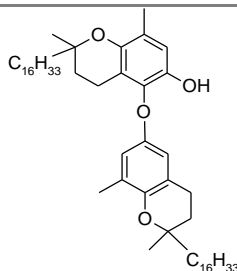
2,2-Methylenebis(5-methyl-6-tert-butyl phenol)



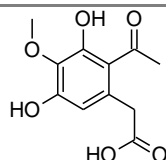
Dihydroauroglucin



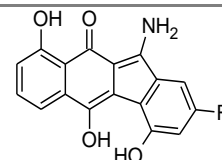
Auroglucin



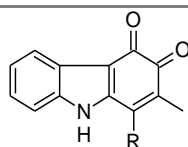
5-(8-tocopheryloxy)-8-tocopherol



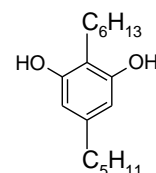
Curvulic acid



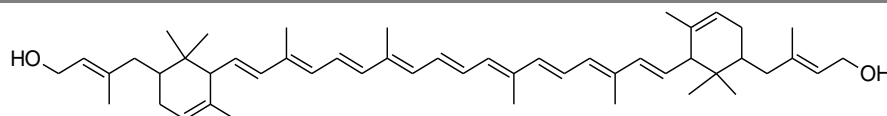
Stealthin A $R_1=OH, R_2=R_3=R_4=R_5=H$
Stealthin B $R_1=R_2=O, R_3=R_4=R_5=H$



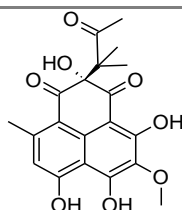
Carbazochinocin A $R= (CH_2)_2CH(CH_3)CH_2CH_3$
Carbazochinocin B $R= (CH_2)_4CH(CH_3)_2$
Carbazochinocin C $R= C_7H_{15}$
Carbazochinocin D $R= (CH_2)_4CH(CH_3)CH_2CH_3$
Carbazochinocin E $R= (CH_2)_5CH(CH_3)_2$
Carbazochinocin F $R= (CH_2)_6CH(CH_3)_2$



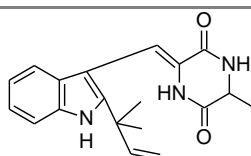
Resortati



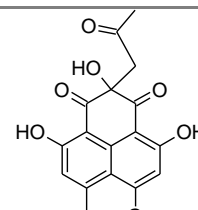
Okadaxanthin



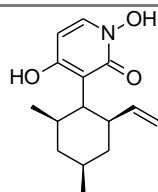
Aurantionone



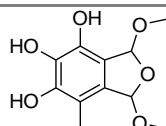
Neochinulin A



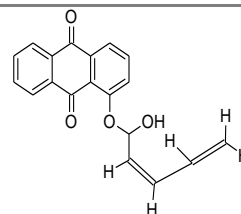
Phenalenedion



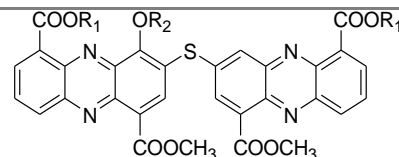
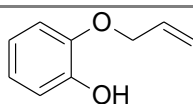
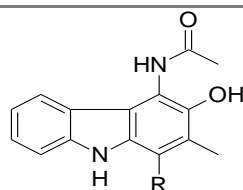
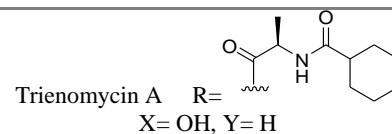
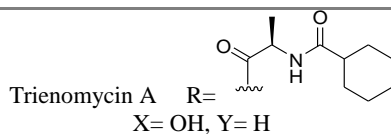
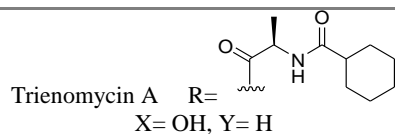
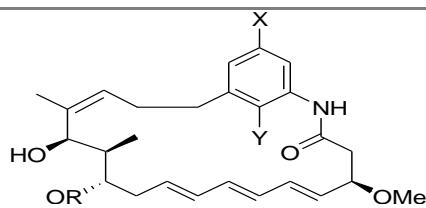
Pyridoxatin



A benzofuran derivatives



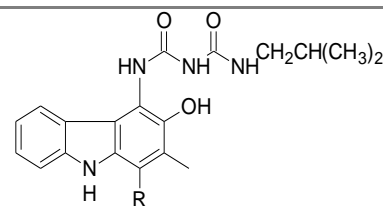
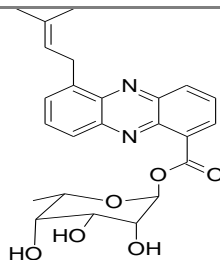
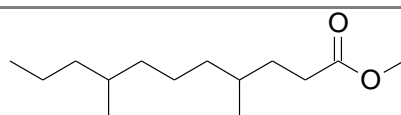
(Z)-1-(1-hydroxypenta-2,4-dien-1-yl)oxyanthracene-9,10-dione



Antionstatin series

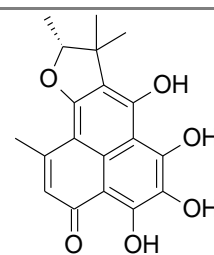
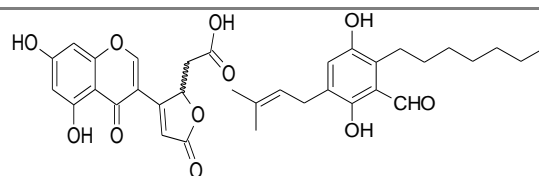
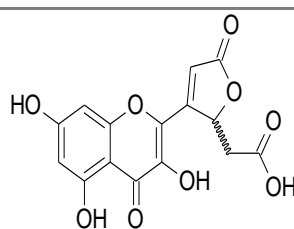
A1, R=(CH₂)₄CH₃
A2, R=(CH₂)CH(CH₃)CH₂CH₃
A3, R=(CH₂)₄CH(CH₃)₂
A4, R=(CH₂)₆CH₃

2-allyloxyphenol

Diphenazithionin R₁ = R₂ = H
R₁=*p*-BrC₆H₄, R₂ = COCH₃

Methyl-4,8-dimethylundecanate

Phenazoviridin

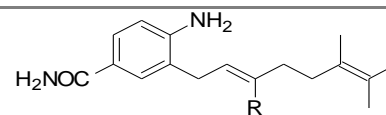
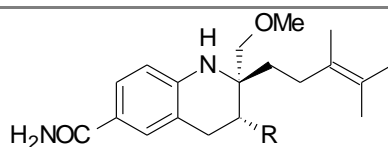
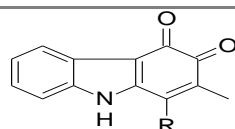
Antionstatin B series
B2, R=(CH₂)₅CH₃& B3, R=(CH₂)₄CH(CH₃)₂
B4, R=(CH₂)₆CH₃ B5, R=(CH₂)₅CH(CH₃)₂

Pochoniolide B

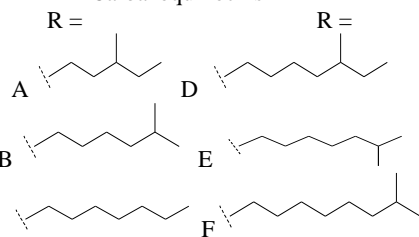
Pochoniolide A

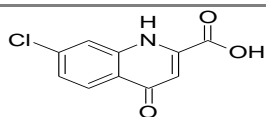
Flavoglucin

Atrovenetin

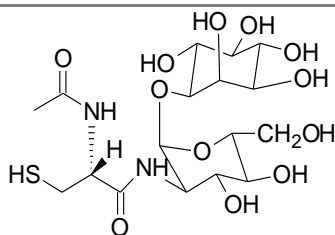


Carbazochinocins A-F

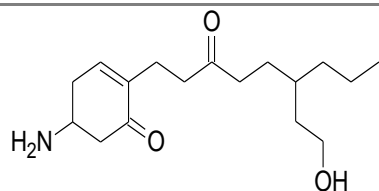
Benzastatins C, R=Cl
Benzastatins D, R=OHBenzastatins A, R=CH₂OMe
Benzastatins B, R=CH₃



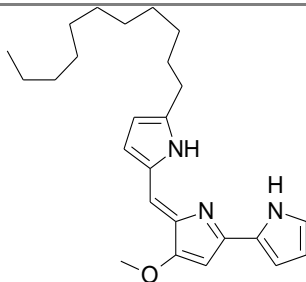
Ageloline A



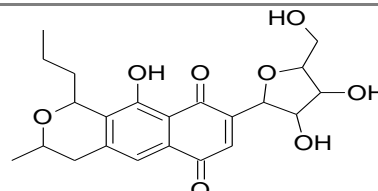
Mycothiol



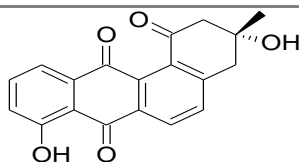
5-amino-2-(6-(2-hydroxyethyl)-3-oxonyl) cyclohex-2-enone



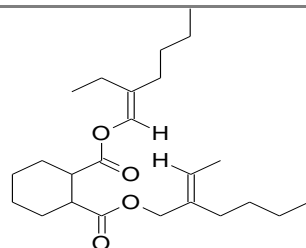
Undecylprodigiosin



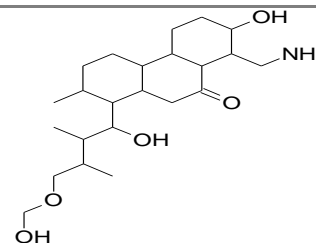
Anhydroexfoliamycin



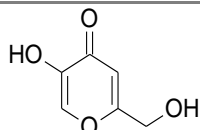
Tetrangomycin



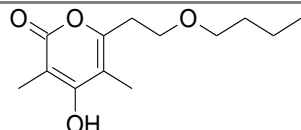
1-((E)-2-ethylhex-1-en-1-yl)2-((E)-2-ethylidenehexyl)cyclohexane-1,2-dicarboxylate



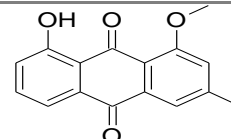
8-(aminomethyl)-7-hydroxy-1-(1-hydroxy-4(hydroxylmethoxy)-2,3-dimethylbutyl)-2-methyl dodecahydrophenanthren-9(1H)-one



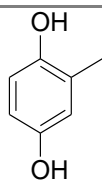
Dihydroxymethyl pyranone



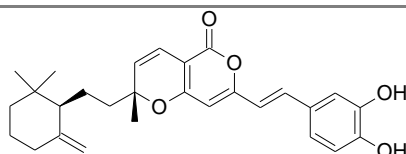
Saccharomonopyrones A



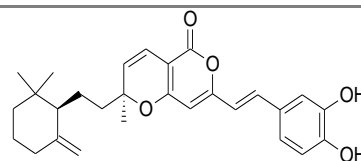
1-methoxy-3-methyl-8-hydroxy-anthraquinone



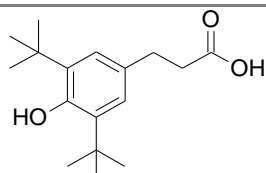
Toluquinol



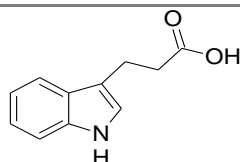
Phellinins A2



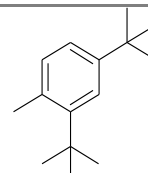
Phellinins A1



Methyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate



1H-Indole-3-propanoic acid



Phenol, 2,4-bis(1,1-dimethylethyl)

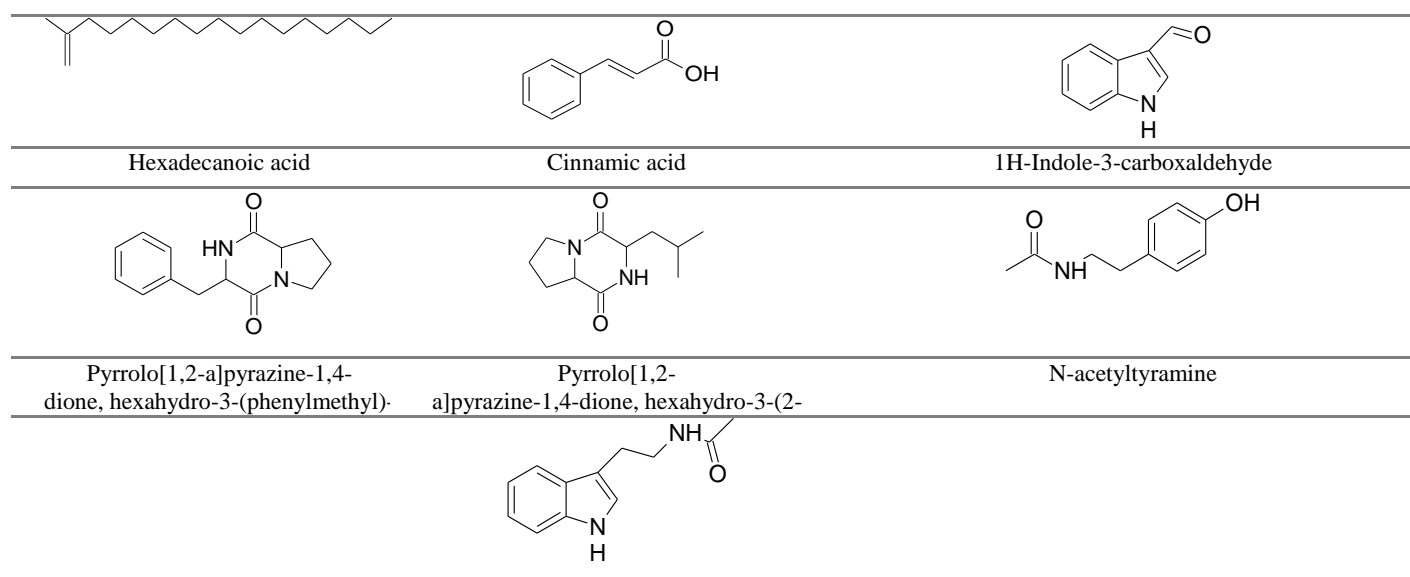


Figure 3. Structures of the microbial-derived antioxidant compounds

1.3.3. Microbial vitamins

Vitamins, as essential micronutrients, include extensive uses in medicine, nutritional, cosmetic and livestock industries. High global demands for vitamins have created great interest in novel production methods. Due to the safety concerns and pollutions during chemical synthesis, green production of vitamins by plants and microbial cell factories has been attracted from the environmental and economic points of view. Vitamins produced by microorganisms are shown in Table 4. Microbial production of vitamins B₂ and B₁₂ has technologically improved and is used on industrial scales; however, others must be developed [34]. Providing desired enantiomeric compounds and being cost-effective and environment-friendly are advantages of microbial production of vitamins [34].

1.3.4. Microbial Pigments

In addition to the safety of microbial pigments in cosmetic and food industry compared to unfavorable characteristics of synthetic coloring agents, other biological characteristics such as antioxidant, antimicrobial and anticancer characteristics have significantly enhanced their uses as food additives [35]. Although plants are the major sources of natural pigments, their cost-effectiveness, stability, unaffectionate by seasonal variations and more importantly amenability to yield improvement characteristics are the major advantages of microbial pigments [36]. Astaxanthin, lycopene, torulene and arpink red are examples of microbial food-grade pigments [37]. Pigment producing bacteria are ubiquitous in extreme environments such as marine [38] and salt [39] regions. Violacein (343.342 g mol⁻¹) is an indole derivative purplish-black pigment produced by various bacterial genera such as *Chromobacterium*, *Janthinobacterium* [40], *Alteromonas*, *Microbulbifer* [41], *Collimonas* [42], *Duganella* [43] and *Pseudoalteromonas* [44]. This bisindole pigment

includes several biological activities, including strong antibacterial, antitumor, anti-protozoan and anti-leishmanial activities. Recently, pigments extracted from marine bacteria with various structures, majorly carotenoids, have been reported to show antioxidant activities [45]. Bacteria that can produce high yields of pigments include strains of *Serratia*, *Achromobacter*, *Sarcina*, *Bacillus* and *Thiackalivibrio*. However, the pigment producing bacteria are more prevalent in the order of *Actinobacteria*, specially the genera of *Rhodococcus*, *Streptomyces*, *Micromonospora*, *Nocardia*, *Actinoplanes*, *Microbispora*, *Thermomonospora*, *Streptosporangium*, *Kitasatospora* and *Actinomadura*. *Streptomyces* is recognized as the genus from which the most diverse pigment producing strains are reported [35,38].

2. Comparative structural diversity of plant and microbial-derived antioxidants

Plant specialized metabolome possesses numerous structurally and functionally varied metabolites of four major pathways, including polyketides, terpenoids, alkaloids, and phenolics. Capacity of antioxidant activity notably depends on the chemical structures, affecting bioavailability of the compounds. Polyphenolics are one of the well-known and great sources of natural antioxidants due to the presence of several hydroxyl groups in their structures [46]. Regarding the distinct structural diversity of flavonoids, antioxidant activity is the best described characteristic of this class of polyphenolics [47]. Huge structural diversity of plant-derived antioxidant metabolites can be attributed to the presence of several sites of ROS generation [47]. It has been suggested that several important antioxidants including phenolic compounds, ascorbic acid and glutathione which are mostly produced by plants may be synthesized as responses to abiotic and biotic stress conditions [48].

Table 2 Bacterial-derived antioxidants

Chemical class	Compound name	Origin	Antioxidant activity	Additional biological activities	Reference
Quinone Pyrrole-type pigment	Anhydroexfoliamycin (416.426 g mol ⁻¹) Undecylprodigiosin (393.575 g mol ⁻¹)	<i>Streptomyces</i> sp.	Reduce ROS levels and enhance antioxidant defenses by increasing catalase activity and glutathione levels	Ameliorates hallmarks of Alzheimer's disease	[85]
Chlorinated quinolone	Ageloline A (223.01261 g mol ⁻¹)	<i>Streptomyces</i> sp. SBT345	Reduces oxidative stress and 4-nitroquinoline-1-oxide induced DNA Damage	Antichlamydial activity	[86]
Cyclohexenon e derivative	5-amino-2-(6- (2-hydroxyethyl)-3-oxonyl) cyclohex-2-enone (295.423g mol ⁻¹)	<i>Streptomyces</i> <i>coelicoflavus</i> BC 01	Exhibit DPPH scavenging and ferric reducing activity	Antimicrobial and anti-inflammatory activities	[87]
Phenanthreno ne derivative-	8-(aminomethyl)-7- hydroxy-1-(1-hydroxy-4- hydroxylmethoxy)-2,3- dimethylbutyl)-2-methyl dodecahydro phenanthren-9(1H)-one (411.2 g mol ⁻¹)	<i>Streptomyces</i> <i>coelicoflavus</i> BC 01	Exhibit DPPH scavenging and ferric reducing activity	Antimicrobial and anti-inflammatory activities	[87]
1,2-cyclohex anedi carboxyl ate derivative	1-((E)-2-ethylhex-1-en-1-yl) 2-((E)-2-ethylidenehexyl) cyclohexane-1,2-dicarboxylate (392.29 g mol ⁻¹)	<i>Streptomyces</i> sp. CAH29	Exhibits DPPH scavenging and ferric reducing activities	Antimicrobial and anti-inflammatory activities.	[88]
Anthraquinon e	Tetrangomycin (322.316 g mol ⁻¹)				
Hydroxy anthraquinoid Extrolite	1-methoxy-3-methyl-8- hydroxy-anthraquinone (268.268 g mol ⁻¹)	<i>Amycolatopsis</i> <i>thermoflava</i> strain SFMA-103	Exhibits DPPH, superoxide, nitric oxide radicals scavenging activity and shows inhibitory effect on lipid peroxidation	Anti-proliferative activity	[89]
Anthracene	(Z)-1-((1-Hydroxypenta-2,4-Dien-1-yl) Oxy)Anthracene-9,10-Dione	<i>Nocardiosis</i> <i>alba</i>	Scavenges DPPH radical	Anti-infection, anticancer & antibiotics	[90]
α -Pyrones	Saccharomonopyrone A (240.1446 g mol ⁻¹)	<i>Saccharo</i> <i>monospora</i> sp. CNQ-490	Exhibits DPPH and ABTS radicals scavenging activity	Not reported	[91]
Phenols	Methyl 3-(3,5-di-tert-butyl-4- hydroxyphenyl) and Propionate (292.419 g mol ⁻¹)	<i>Kribbella</i> sp. UTMC 267	Not reported	Not reported	[92,93]
Indole	1H-Indole-3-propanoic acid (189.2105 g mol ⁻¹)		Exhibits 2,2v-azino-bis-3-ethyl- benz-thiazoline6-sulfonic acid scavenging activity and inhibitory effect on lipid peroxidation in rat striatum	Neuroprotective activity	[93-95]
Phenols	Phenol, 2,4-bis(1,1-dimethylethyl) (206.329 g mol ⁻¹)	<i>Kribbella</i> sp. UTMC 267	Not reported	Antimicrobial activity	[93,96,97]
Long-chain fatty acids	Hexadecanoic acid (256.4 g mol ⁻¹)		Not reported	Not reported	[93,98]
Cinnamic acids	Cinnamic acid (148.1586 g mol ⁻¹)	<i>Nocardia</i> sp. UTMC 751	Exhibits DPPH scavenging activity	Antimicrobial	[93,99]
Indole	1H-Indole-3-carboxaldehyde (145.161 g mol ⁻¹)		Exhibits DPPH scavenging activity Inhibitory effect on microsomal lipid peroxidation (LPO)	Not reported	[93,100]
Diketopiperazi ne derivative	Pyrrolo[1,2-a]pyrazine-1,4- dione, hexahydro-3-(phenylmethyl)- (244.294 g mol ⁻¹)		Exhibits DPPH scavenging activity	Not reported	[101,102]
Diketo piperazine derivative	Pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro- 3-(2-methylpropyl) (210.2728 g mol ⁻¹)	<i>Nocardia</i> sp. UTMC 751	Exhibits DPPH scavenging activity	Not reported	[101,102]
Alkaloid	N-acetyltyramine (179.219 g mol ⁻¹)	<i>Actinokineospor</i> <i>a</i> sp. UTMC 968	Exhibits DPPH scavenging activity	Not reported	[103]
Alkaloid	N-acetyltryptamine (202.257 g mol ⁻¹)	<i>Actinokineospor</i> <i>a</i> sp. UTMC 968	Exhibits DPPH scavenging activity	Not reported	[103]

Table 3 Fungal-derived antioxidants

Chemical class	Compound	Origin	Antioxidant activity	Additional biological activity	Reference
Phenolic compounds	2,2-Methylenebis (5-methyl-6- <i>tert</i> -butyl-phenol) (340.507 g mol ⁻¹)	<i>Penicillium janthinellum</i>	Antioxidative properties on linoleic acid peroxidation	Not reported	[104]
Dihydroxy pyridins	Pyridoxatin (263.337 g mol ⁻¹)	<i>Acromoin</i> sp.	Inhibits free radicals induced lipid peroxidation in rat liver microsomes	Antimicrobial and anticancer Activities	[105,106]
γ -Pyrone derivative	Dihydroxymethyl pyranone (142.11 g mol ⁻¹)	<i>Aspergillus candidus</i>	Exhibits DPPH scavenging activity	Antimicrobial, antiviral and antitumor Activities	[107]
Styrylpyrones	Phellinins A1 (448 g mol ⁻¹) Phellinins A2 (448 g/mol)	<i>Phellinus</i> sp.	Exhibits DPPH and superoxide scavenging activity	Not reported	[108]
Chromone derivatives	Pochoniolides A and B (318.46 g mol ⁻¹)	<i>Pochonia chlamydozoria</i> var. <i>spinulospora</i> FKI-7537	Exhibit hydroxyl radical-scavenging and singlet oxygen-quenching activities	Not reported	[109]
Methylhydro Quinone	Toluquinol (124.139 g mol ⁻¹)	<i>Penicillium</i> sp.	Shows ABTS and DPPH scavenging activity	Anti-cancer	[110]
Isobenzofuran	Isopestacin (272.25 g mol ⁻¹) Pestacin (258.27 g mol ⁻¹)	<i>Pestalotiopsis microspore</i>	Inhibition of oxidation of α -Keto- γ -methiolbutyric acid	Antifungal and antimycotic activities	[111,112]
Phenolic compound	Graphislactone (302.28 g mol ⁻¹)	<i>Microsphaeropsis olivacea</i>	Active towards the tyrosine Kinase	Not reported	[113]
Isobenzofuran one Derivative	4,6-dihydroxy-5-methoxy-7-methyl-1,3-Dihydroisobenzofuran (196.2 g mol ⁻¹) 4,5,6-trihydroxy-7-methyl-1,3-dihydroisobenzofuran (196.16 g mol ⁻¹) 4,6-dihydroxy-5-methoxy-7-Methylphthalide (210.18 g mol ⁻¹)	<i>Cephalosporium</i> sp.	DPPH radical-scavenging Activity	Not reported	[114]
Coumarin derivative	Versicolones A and B	<i>Aspergillus versicolor</i>	Scavenge ABTS	Not reported	[115]
Quinone epoxide	Terremutin (156.14 g mol ⁻¹) Terreic acid (154.12 g mol ⁻¹)	<i>Aspergillus terreus</i>	Scavenges hydrogen peroxide radical and inhibit and lipid peroxidation	Antibacterial activity	[116]
Polyphenols	Inonoblins A, B, C (462.42g mol ⁻¹) and Phelligridins D, E, G	<i>Inonotus obliquus</i>	Strongly scavenge ABTS and DPPH, and moderately suppress the superoxide radical anion	Antifungal and anticancer activities	[117]
Azaphillone class	Sclerotiorin (390.9 g mol ⁻¹)	<i>Penicillium sclerotiorum</i> <i>Penicillium frequentans</i>	Uncompetitively inhibit soybean lipoxygenase-1	Not reported	[118]

Although plants are well-known sources of active compounds with various pharmaceutically bioactivities, a significant number of novel and bioactive metabolites were achieved from microorganisms [29,49,50]. Therefore, it can be suggested that microorganisms can produce a significant range of antioxidants as discussed.

Structural diversity of microbial compounds with antioxidant activity is associated with various structural classes, including carotenoids, indoles, phenolic compounds, phenazine, isoflavonoids, macrolide and quinolone [51].



Table 4 Vitamins with antioxidant activity produced by microorganisms

Vitamins	Microbial sources	References
Vitamin A (286.4 g mol ⁻¹)	<i>Escherichia coli</i>	[119]
	<i>Yarrowia lipolytica</i>	[120]
Vitamin D (384.7 g mol ⁻¹)	<i>Saccharomyces cerevisiae</i>	[121]
	<i>Rhodococcus erythropolis</i>	[122]
Vitamin E (430.7061 g mol ⁻¹)	<i>Euglena gracilis</i>	[123]
	<i>Stichococcus bacillaris</i>	[124]
	<i>Saccharomyces cerevisiae</i>	[125]
Vitamin K (450,68 g mol ⁻¹)	<i>Bacillus subtilis</i> var.natto	[126]
	<i>Bacillus subtilis</i>	[127]
Vitamin B1 (265.355 g mol ⁻¹)	<i>Bacillus subtilis</i> TH95	[128]
	<i>Escherichia coli</i>	[129]
	<i>Aspergillus oryzae</i>	[130]
Vitamin B2 (376.36 g mol ⁻¹)	<i>Bacillus subtilis</i>	[131]
	<i>Ashbya gossypii</i>	[132]
	<i>Candida famata</i>	[133]
Vitamin B3 (127.135 g mol ⁻¹)	<i>Saccharomyces cerevisiae</i>	[134]
	<i>Escherichia coli</i>	[135]
Vitamin B5 (219.24 g mol ⁻¹)	<i>Corynebacterium glutamicum</i>	[136]
Vitamin B6 (247.1 g mol ⁻¹)	<i>Bacillus subtilis</i>	[137]
Vitamin B7 (244.31 g mol ⁻¹)	<i>Agrobacterium/ Rhizobium</i> HK4	[138]
Vitamin B9 (441.404 g mol ⁻¹)	<i>Ashbya gossypii</i> (ATCC 10895)	[139]
Vitamin B12 (1355.36 g mol ⁻¹)	<i>Sinorhizobium meliloti</i> (MC5-2)	[140]
	<i>Propionibacterium shermanii</i>	[141]
Vitamin C (176.124 g mol ⁻¹)	<i>Ketogulonicigenium vulgare</i> DSM 4025	[142]
	<i>G. oxydans</i> and <i>Ketogulonicigenium vulgare</i> and <i>Bacillus endophyticus</i>	[143]
	<i>Xanthomonas campestris</i> 2286	[144]

This shows that the spectrum of the antioxidant metabolites varies in chemical structures, highlighting the importance of microorganisms as resources of antioxidants. Several promising antioxidants such as pestacin, astaxanthin, polysaccharides and isopestacin are collected from fungi, acting as functional ingredients in food and cosmetic industries as well as pharmaceutical products [51]. Furthermore, the discovery of various redox signaling proteins in *Saccharomyces* spp. opens further routes for bioprospecting because of numerous industrial and food uses (dietary supplements) of yeasts [52]. Overall, Actinobacteria, cyanobacteria, lichens and fungi are prominent antioxidant sources [29]. Twelve types of vitamin structure in eukaryote and prokaryotic sources include antioxidant activity. Types of the structures described in plants with antioxidant activity in literature reach 58 with a molecular weight range of 108.1 Da (*p*-cresol) to 602.9 Da (γ -oryzanol). However, most of the antioxidant compounds produced by plant species (74%) include a molecular size of less than 500 Da. For microbial-derived antioxidants, 21 compounds have been described from algae, 19 from fungi and 44 from bacteria. Molecular size of the microbial antioxidants varies from toluquinol with 124.1 Da to a macrolide antibiotic (PC-766 B) with 777.0 Da, while a number of the antioxidant skeletons are only produced by the microbes.

Based on this review, the most prevalent type of antioxidant compounds produced by plants belongs to the simple phenolics, phenolic acids, flavonoids, anthocyanins, tannins, phenolic diterpenes, components of essential oils, lignans, avenanthramides, carotenoids, and oryzanols. Although phenolic-derived compounds includes the largest

group in plants and microorganisms, they seem further investigated in plant sources. Antioxidants with flavonoid skeleton rank the second group of bioactive classes of plant metabolites, while the bioactive microbial metabolites are majorly phenazine and quinone-derived compounds. Additionally, antioxidant structural types of phenazine, carbazol, indoles, and macrolides are more diversely produced by bacteria than plants. This comparative review shows that despite long-term investigation of plant antioxidants and the superiority of antioxidants derived from plants that are rich in vitamins, carotenoids and phenolic compounds, various groups of antioxidant metabolites such as phenolics, carotenoids alkaloids and terpenes and novel rare structures such as phenazine derivatives, benzastatins and benzenediols or combined structures such as exopolysaccharides with various functional groups are discovered from microorganisms.

3. Use of natural antioxidants, privilege of microbial-derived antioxidants

In addition to the medicinal importance of antioxidants, these nutraceuticals are widely used in food industries. Oxidation prevention, free radical neutralization, flavor and color enhancement and food packaging and preservation are the major reasons for this widespread use. Recently, Gremski et al. formulated antioxidants-rich ice creams with improved storage stability containing herbal antioxidants such as quercetin-3-rutinoside, 5,7-dihydroxyflavone, hesperidin and caffeic acid [53]. Smart packaging using biopolymers is another use of antioxidants for shelf life extension of

products to delay the deterioration of products in meat industry due to the high susceptibility of meats to lipid oxidation [54]. Color changes in presence of pH indicator in these active coatings cause rapid food spoilage. These active coatings seem to be eco-friendly, safer and cost-effective, compared to synthetic coatings for the packaging [55] and feed [56] industries. Microbial antioxidants, specially L-ergothioneine, β -carotene and polyphenols, are used in cosmetic industries due to decreased risks of side effects or allergies [57] as well as use of antioxidant producing microbes and plant probiotic bacteria due to amending soil fertility and grain quality [58].

Antioxidants are collected using solvent-based extraction or chemical synthesis, which both are often exhausting, non-profitable, energy-intensive and detrimental to the environment due to their relatively low-levels of antioxidants in tissue plants, uncontrolled seasonal and geographic variabilities of plants and hazardous waste generation in their extraction. Cost-effective production of microbial antioxidants due to the low-cost substrates and their rapid growth can respond to increasing consumer demands for natural antioxidants. Furthermore, microorganisms secrete antioxidants into the liquid media through their extracellular enzyme activities, causing low-cost downstream fermentation processing [59]. In addition, microbial production of antioxidants can be enhanced through genetic manipulation of microorganisms, adaptive laboratory evolution and optimization of intrinsic biosynthetic pathways [60]. The overall high-molecular weight of the microbial-derived antioxidants can be preferred in bioseparation processes. Unlike synthetic antioxidants, these natural antioxidants include low or no toxicities for humans and environment and their production technology is a clean, sustainable and reused technology [29]. Existence of various functional groups such as carbonyl and methylene groups, reactive NeH (carquinostatin A, carbazole and phenazinehetero cycles, benzastatins, JBIR-94 and JBIR-125), OeH groups (carquinostatin A, benthocyanins A, B, C, benzastatins, phelligridins D, E, G and inonoblins A, B, C) and methoxy groups (benzastatins) highlight diversity of microbial antioxidants [51]. Nevertheless, further studies are necessary to improve challenges during the development of food-grade microbial antioxidants such as limiting the production of unwanted interfering compounds by a better understanding of the natural antioxidant mechanisms of action.

4. Conclusion

The imbalance between antioxidant defense and reactive species production is a critical issue, evolving numerous diseases by causing damages to the genome and various macromolecules. It has frequently been reported that higher consumption of antioxidants as dietary supplements decreases the risk of various diseases. Moreover, nutraceuticals with natural ingredients such as antioxidants are

essential in the food category. Therefore, global needs for promising antioxidants have increased. Regarding high quantities (nearly 60%) of available natural drugs and well-documented ranks of microbial nutraceuticals, especially antioxidants, environmental-friendly antioxidant production techniques from nature must be developed. The vast diversity of microorganisms, non-toxic metabolites, structurally varied metabolites such as antioxidants and more-efficient production of antioxidants that are more readily manipulated compared to plants or synthetic antioxidants highlight the microorganisms as potential producers of natural antioxidants.

Phenolic and terpenoids are the dominant structural groups of plant antioxidants and widespread overlaps of antioxidants produced by fungi and algae. Nevertheless, antioxidant activity of bacteria originates from the most structural skeleton diversities, including carotenoids, phenazine derivatives, phycobiliprotein, polyketides and polysaccharides, which contain reactive hydroxyl groups or possess at least an extra functional group in addition to hydroxyl group. Generally, antioxidant compounds containing O–H have higher activity compared to those containing N–H group, owing to less energy in bond-dissociation. The level of antioxidant activities of plant and microorganism-derived antioxidants differ depending on their reactive groups, including reactive N–H, C=O groups and hydroxyl, which can react with free radicals. Ellagic acid, ferulic acid and gallic acid, are potential fungi-derived antioxidants that include two to four hydroxyl groups. Zeaxanthin and astaxanthin are prevalent microbial antioxidants with conjugated-chain harboring hydroxyl groups. Moreover, microbial exopolysaccharides demonstrate antioxidant activities by having various functional groups such as reactive hydroxyl, aldehyde and ketone groups, which may be exposed for reaction with free radicals.

From microorganisms, various genera of Actinobacteria efficiently produce antioxidants; from which, *Streptomyces* is the dominant genus. It is noteworthy that other biological activities such as antimicrobial and antitumor activities have been reported by microbial antioxidants. Since the bioactivity of antioxidants may decrease during food processing, thermostable antioxidants derived from thermophilic microorganisms may help solve this problem. In addition to various antioxidant structures, the real biodiversity of microorganisms is still poorly known, which can be further investigated for human benefits. Despite the fact that a large proportion of the plant antioxidants are well-known, other microbial antioxidants must be studied. This survey more clearly shows the competency of microbial bioactive metabolites as the major sources of antioxidants in industries, mainly food industries. A promising approach in the discovery of novel microbial antioxidants is the microbial cost-effective small-genome analysis, compared to the large complicated genomes (haploids) of plants. This review has



summarized various structures of naturally-derived antioxidants and the importance of natural microbial antioxidants as innovative sources of bioactive molecules. Moreover, current review suggests the future prospects of microbial antioxidants for the commercial production of safer and more-effective antioxidants. Elucidating structural and physicochemical characteristics of the microbial antioxidants enables the discovery of novel antioxidants as well as describing their mechanisms of action, which can lead to development of novel production strategies in target industries.

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6. Conflict of Interest

The authors report no conflicts of interest.

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مرور جامع بر متابولیت‌های ثانویه گیاهی و میکربی واجد فعالیت ضداکسیدانی

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تاریخچه مقاله

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پذیرش ۲۶ فوریه ۲۰۲۲

واژگان کلیدی

- ضداکسیدان‌های باکتریایی
- تنوع شیمیایی
- ترکیبات زیست‌فعال میکربی
- متابولیت‌های ثانویه گیاهی

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چکیده

سابقه و هدف: اختلال ناشی از گونه‌های فعال حاصل از فرآیندهای مختلف فیزیولوژیکی یا بیوشیمیایی باعث آسیب به سلول‌ها شده و منجر به آپوپتوز سلولی می‌شود. علاوه بر اهمیت پزشکی، ترکیبات با خاصیت ضداکسیدانی از تولید رادیکال‌های آزاد و ایجاد مساله در صنایع غذایی نیز جلوگیری می‌کنند. علاوه بر این، ضداکسیدان‌ها را می‌توان به عنوان نگهدارنده‌های با ارزش غذایی در نظر گرفت که علاوه بر به تعویق انداختن فساد مواد غذایی، ارزش غذایی آن را از طریق جلوگیری از اکسیداسیون محتویات مختلف ارتقاء می‌دهند. با توجه به هزینه بالا و اثرات خطرناک گزارش شده از ضداکسیدان‌های سنتزی بر سلامت انسان، جستجو برای ترکیبات ضداکسیدانی طبیعی افزایش یافته است. بنابراین، هدف این مقاله مروری، بررسی کلی ضداکسیدان‌های طبیعی گیاهان و میکروارگانیسم‌ها، همچنین تنوع و کاربردهای صنعتی آن‌ها است.

یافته‌ها و نتیجه‌گیری: گیاهان و میکروارگانیسم‌ها منابع طبیعی مهم حاوی ضداکسیدان‌های مختلف هستند. با این وجود، تنوع گسترده میکروارگانیسم‌ها و متابولیت‌های آنها و همچنین سهولت دستکاری آنها در مقایسه با گیاهان با روش‌های سنتزی حاکی از این است که باید تکنیک‌های تولید ضداکسیدان سازگار با محیط‌زیست توسط میکروارگانیسم‌ها تجدید نظر شوند. فنول و ترپنوئیدها ضداکسیدان‌های غالب در گیاهان، قارچ‌ها و جلبک‌ها هستند، در حالی که ضداکسیدان‌های باکتریایی بسیار متنوع و شامل کاروتنوئیدها، پلی‌کتیدها، پلی‌ساکاریدها هستند. در این مقاله مروری به وضوح شایستگی متابولیت‌های زیست‌فعال میکروبی به عنوان منابع نوآورانه‌ی تولید ضداکسیدان‌ها در آینده برجسته می‌شود. بررسی ویژگی‌های ساختاری و فیزیکیوشیمیایی ضداکسیدان‌های میکروبی می‌تواند کشف آنتی‌اکسیدان‌های نوظهور و مکانیسم‌های عملکرد آن‌ها را میسر سازد، که در نهایت منجر به ظهور استراتژی‌های متنوع در صنعت خواهد شد.

تعارض منافع: نویسندگان اعلام می‌کنند که هیچ نوع تعارض منافی مرتبط با انتشار این مقاله ندارند.