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Review Article

Potential dyes from edible mushrooms for human health

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Abstract: Colors (dyes or pigments) have been applied in many sectors of human life, such as textile industries, food, and medicine, thus becoming a crucial factor that cannot be neglected. The origin of color can be obtained from nature or synthetic sources. Nowadays, synthetic colors are used more often than natural ones. However, the use of synthetic colors needs to be considered as they have the potential to cause health problems and contribute to waste issues. On the other hand, natural color sources are dominated by the plant kingdom, such as mushrooms, which are advantageous for health, more economical, and environmentally friendly. The method used in this review was to explore the literatures that discus dyes or pigments from macrofungi or mushrooms. Furthermore, the dyes or pigments were classified from edible or medicinal mushroom, then dyes or pigments were categorized based on their chemical structure. Mushrooms of various genera and species produce different colors that belong to constituent melanin, terpenoids, carotenoids, quinone, styrylpyrone, azulene, and pteridine. Therefore, natural colors are very promising for application in human health, due to their active compounds potency as anticancer, anti-HIV, antioxidant, and antimicrobial. In addition, pigments containing azulene structures from mushrooms are developed as solar cells and UV protection.

Keywords: Color, Dyes, Health, Mushroom, Pigments.

INTRODUCTION

Coloring agents have been involved in many areas of human life, and we can distinguish things through shapes and colors. The application of color is inseparable from life since it is involved in the textile industries, painting, photography, food, and beverages such as yeast for making beer, bread, meat, and medicine.[1] Plants are the main natural source of color and the most widely used coloring agent, but plants have many limitations including the different weather and geography. Due to the intensity and stability of synthetic colors after washing as well as the fact that they were unaffected by changing weather and geography, synthetic colors began to replace many natural colors by the end of the 1900s. Nevertheless, synthetic colors have some problems, especially regarding environmental waste that induces cancer; therefore motto "back to nature" is back to life.[2,3,4]

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There are two types of colors: dyes and pigments with the main difference in their solubility. Dyes are soluble in water, while pigments are inorganic and organic compounds which is insoluble in water. The diameter of pigments around 1-2 microns suggested a microscope to see it.[5,6] According to the origin, the color can be derived from natural or synthetic sources. The natural color can be produced from plants, animals, and mushrooms. The term mushroom is used to refer to only the fruiting bodies of fungi that are usually used for food. In comparison fungi mention the overall bodies, including the fruiting bodies and the underground.[7] Both micro- and macrofungi can produce the natural color. In the Greek language, macros mean large; therefore macrofungi can be seen by the eyes. On the other hand microfungi need a magnifying glass to be observed.[8] The synonym of macrofungi is mushroom.[9]

One of the famous microfungi is *Monascus* sp., which gives the red color to red rice (angkak). Microfungi like *Aspergillus ochraceous, A. sulphureus*, and *A. glaucus* make viopurpurin, which gives things their purple color. *Monascus* sp. gives things their red color from canthaxanthin and ankaflavin compounds. *Aspergillus* sp. also produces viomellein, which gives a reddish brown color, catenarine (red color), and variecolorquinone (yellow color).[4]

REVIEW METHOD

This review started with collecting some literatures from Pubmed (107), Frontiers (1133), and Springer (1755). The keywords were ("Pigments" OR "dyes") AND (from); AND ("Edible"); AND ("Mushroom" OR "Macrofungi"). The articles have been collected then selected using inclusion criteria including full-text accessability and the articles containing the chemical structure. The exclusion criteria were articles not relevant to the topic and articles containing molecular biology and genetics.

RESULTS AND DISCUSSION

MELANIN

The first step of selecting suitable solvents for extraction depends on their polarity and chemical structures. For aglycones structure, the medium polarity until less polarity solvents are preferable but if the glycosylated structure requires more polar solvents. Many extraction techniques are performed at room temperature or at a higher temperature. The popular one is maceration because it can be done at room temperature with an simple procedure. The other methods of extraction are percolation, soxhlet, reflux, ultrasound, supercritical fluid, and microwave.[10] Melanin is a polymer with insoluable characteristics in water, organic solvents, and cold or hot acids. Moreover, any modification to improve the dissolution potentially disarrangess the structure. Nevertheless, melanin is soluble in alkali and can be bleached by oxidizing agents. Thus, with its special characteristics, melanin is challenging to be isolated.[11,12]

There are three pathways producing melanin in fungi (Figure 1). The first pathways to produce 1,8-dihydroxy naphthalene (DHN) start with *malonyl CoA* or *acetyl* CoA precursor. DHN-melanin is melanin without nitrogen in its structure. The second-way melanin is by *glutaminyl-hydroxybenzene* (GHB), which is made when the tyrosinase enzyme changes. The third-way melanin is made from the amino acids eumelanin and pheomelanin.[13] *Agrocybe cylindracea* produces the melanin coloring agent, which gives a dark color. According to data from *Fourier transform infrared spectroscopy* (FTIR) and UV-Vis, the 3,4-dihydroxyphenylalanine melanin groups that *A. cylindracea* produces are structurally similar to synthetic tyrosine melanin.[14] There are 4 forms of melanin, including allomelanin (blue), GHB-melanin (green), eumelanin (pink), and pyomelanin (red).[4] *According to Kim et al. (1997), A. cylindracea also makes the indole colors 6-hydroxy-1H-indole-3-acetamide and 6-hydroxy-1H-indole-3-*

carboxaldehyde. These can stop lipid peroxidation in rats with IC_{50} of 3.9 and 4.1 µg/ml.

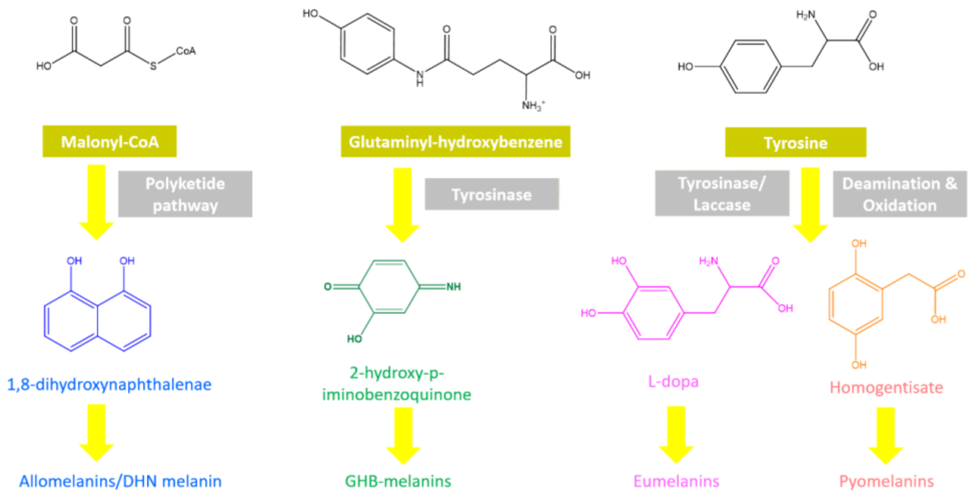

Figure 1. Pathways of melanin production

TERPENE

Terpene possesses varied structures from linear to cyclic, with a low molecular weight to a high molecular weight, volatile to non-volatile, simple terpene into modified terpene. Different terpene structures can induce different polarities, thus requiring particular extraction techniques. The structure of linear terpene or cyclic terpene commonly comprises hydrocarbons. The longer the hydrocarbon chain, the more solubility to non-polar solvents. Monoterpene or sesquiterpene with carbons less than 15 tends to be volatile and has low polarity and low molecular weight. Mostly, the volatile terpene can be extracted using distillation or organic solvent or even modern ones such as microwave-assisted extraction (MAE). The longer hydrocarbon chain will affect their elution. For example, a terpene with longer carbon chains will elute faster than with shorter ones. Still, the unique one is that cyclic terpene will eluate earlier than non-cyclic terpene, even though they have the same number of carbons. This happened because cyclic terpene gives a more compact structure to be eluated.[16]

Terpene is one of the metabolite substances that macrofungi produce with the basic structure of isoprene. Terpenes are classified into:[17]

a. Monoterpene : 2 units isoprene or 10 atoms of carbon (C_{10})
b. Sesquiterpene : 3 units isoprene or 15 atoms of carbon (C_{15})
c. Diterpene : 4 units isoprene or 20 atoms of carbon (C_{20})
d. Triterpene : 6 units isoprene or 30 atoms of carbon (C_{30})
e. Tetraterpene : 8 units isoprene or 40 atoms of carbon(C_{40})

Terpene constituents from fungi have been used for a long time to increase human health. Ganoderma (Reishi) has been recorded since ancient times as a medicinal mushroom in China as well as in Japan to increase the immune system. In the book of *Shennong Bencaojing* and *Chinese Pharmacopeia* (2010), Ganoderma is documented as a medicinal mushroom.[18] Colossolactone V-VIII compounds contain the skeleton structure of steroid terpenoid from *G. colossum* that inhibit HIV-1 protease with IC_{50} of 5-13 ppm while a yellow oil, ganomycin I, showed IC_{50} of 7.5 ppm.[19,20] In vitro, ergosterol, ergosterol peroxide, and 5,6-dehydroergosterol isolated from *G. lucidum* could inhibit breast cancer MDA-MB-231 (*triple negative breast cancer*) by decreasing the expression of cyclin D1, AKT1, AKT2, dan BCL-XL.[21] A yellow powder, leucocontextin D and L, have been successfully isolated from *G. leucocontextum* and leucocontextin E, a yellow oil, showed its activity against endocervical cancer SMM-7721, leukemia cancer K562, and breast cancer MCF-7.[22]

Besides terpenes, fungi also produce meroterpenoids with different kinds of structure and color thus having different pharmacological activities. Meroterpenoids have at least two main structures. Terpenoids structure come from the mevalonate pathway, and the non-terpenoids structure comes from pathways like shikimate, amino acid, polyketide, and more. There are also four parts to the non-terpenoid structure: the shikimate-terpenoid moiety, the indole-terpenoid moiety, the polyketide-terpenoid moiety, and others.[23] One of the edible mushrooms that synthesize meroterpene is *Albatrellus fletti* which also produces grifolin, neogrifolin, and confluentin. The IC_{50} of grifolin, neogrifolin, and confluentin were around 24 up to 35.4 µM for colon cancer HT-29 and SW48 and also cervix cancer HeLa cells. The purple oil, albatrellin, from *A. confluens* was able to kill lung cancer Hep52 cells with an IC_{50} 1.55 µM.[24,25] Another purple oil called grifolinone B was found in *A. caeruleoporus* and it was able to stop the production of nitric oxide (NO) triggered by lipopolysaccharide with an IC_{50} value of 22.9 µM.[26] In Finland, *A. ovinus* is categorized as an edible mushroom and is usually used as a culinary ingredient because it contains a lot of minerals.[27]

CAROTENOIDS

Carotenoid pigments are part of terpene, especially tetraterpene (C_{40}), found in many plants, photosynthetic bacteria, algae, animals, and mushrooms. Isolating carotenoids is exciting due to the complexity of the pigments and the matrix. Carotenoids are very sensitive to heat, light, acids, oxygen, and long-time exposure extraction. The advisable solvent to extract is a non-polar solvent for non-polar carotenoids, whereas polar solvents are more suitable to extract the more polar carotenoids. The presence of water in the matrix can disrupt the extraction steps. The water can be removed by boiling or heating, but it will degrade and isomerize the structure of carotenoids. In order to minimize the water content and to protect the carotenoids, the matrix can be dehydrated by freeze drying method. However, if the matrix also presents a mixture of water-soluble compounds and sugar, it must be separated first before the freeze-drying step.[28]

The characteristic feature of carotenoid is the presence of chromophore functional groups that reflect red, yellow, and orange color in fruits, vegetables and more than 600 isomers have been found. *Chantarellus cibarius* is commonly called “Golden chanterelle” because the color of the cap is golden yellow until orange due to the presence of canthaxanthin. The compound canthaxanthin belongs to the carotenoids that are easy to degrade by heating or drying. *C. enelensis* is “Albino chanterelle” which lack canthaxanthin thus gives white fruiting bodies but still has an apricot scent like “Golden chanterelle” and is edible.[29] The ability of carotenoids to bind radical scavengers allows for their identification.[30] In addition to being an antioxidant, the methanol extract from *C. cibarius* was also able to fight cervical adenocarcinoma HeLa, breast cancer MDA-MB-453, and leukemia K562. The methanol extract can also inhibit *angiotensin-converting enzyme* I (ACE) to decrease blood pressure by 0.063 ppm. The methanol extract is also potent against gram-positive bacteria especially *E. faecalis.*[31]

Carotenoids in *Cordyceps militaris* turned the fruiting bodies of these fungi from yellow to orange. However, some albino *Cordyceps* have also evolved due to mutations.[32] *Cordyceps* sp. is a rare fungus that lives in high mountains, primarily in Bhutan and Nepal at elevations ranging from 3400 to 4100 feet and temperatures ranging from -10°C to -20°C. *Cordyceps* comprises two Greek words: “cord” or “club” means lower part, and “ceps” or “head” means upper part since these fungi live in the head of a worm (*Hepialus armoricanus*). *Cordyceps* sp. is an entomopathogenic fungus with many popular names such as “Chinese

Caterpillar Fungus" and "Worm in Winter and Grass in Summer".[33] This rare mushroom has been shown to maintain the immune system and cure chronic diseases. The existence of these fungi has become very scarce due to the complex life cycle of the worm and the environment. The hunting of *Cordyceps* sp. was forbidden until 2003, was just legalized in 2004, and became the main livelihood for the society living in the mountains.[34,35]

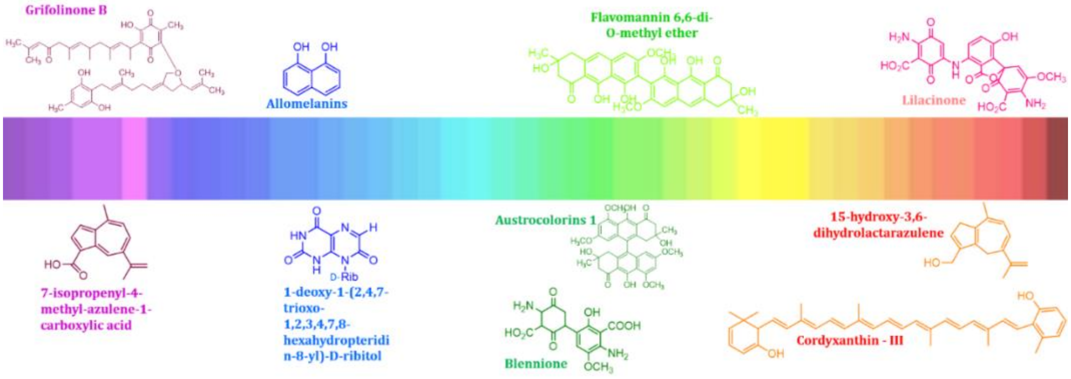

Figure 2. The variety of chemical structures yielded from mushrooms

UV radiation from sunlight and blue light from electronic gadgets could destroy the retina. Supplementation of extract water of *C. militaris* twice a day at 10 mg/kg could protect the retina from those lights by decreasing the hypertrophy of Muller cells and increasing the GSH level to accelerate the functional recovery of visual acuity and sensitivity. The major compound from the water extract was cordyxanthin, which has a similar structure to that of carotenoids (Figure 2). The structure of cordyxanthin is unique compared to other carotenoids since it contains more hydroxyl groups than carotenoids, making it more soluble in water.[36] Moreover, *Cordyceps* sp. is also rich in ergothioneine, cordycepin, γ-aminobutyric acid (GABA), polysaccharides, and other important compounds for therapy or as *functional foods* to stay healthy. Cordycepin became the most wanted antivirus during COVID-19.[37]

QUINONE

There are two forms of anthraquinones: aglycones and glycosylated anthraquinones. For aglycones, they can be extracted using less polar solvents, whereas the glycosylated anthraquinones will be suitable to be extracted using more polar solvents. Interestingly, anthraquinone can be soluble in alkaline; thus, the color can be used as a guideline to distinguish anthraquinones or, anthrones or dianthrones. Hydroxyls that attach to position numbers 1 and 2 of anthraquinone in an alkaline solution will give a blue-violet color, while substitution in position numbers 1 and 8 has a red color. The yellow color of anthrones and dianthrones in an alkaline solution will quickly turn to red color. Acid can be used to hydrolyze the glycosylated anthraquinones into free anthraquinones, but some C-glycosides are resistant to being hydrolyzed.[10,38]

Quinones are two keto groups at positions 9 and 10 that define the skeleton structure of anthraquinones, which derive from anthracene. More than 700 anthraquinones and their derivatives have been found with color gradations ranging from green yellowish to green blueish.[39,40] Anthraquinone structure dominated the variety of color in mushrooms.[41] *Cortinarius* sp. is also one of the mushrooms producing anthraquinone. Citreorosein 6,8-dimethyl ether gives an orange color; 1-hydroxy-3-methyl-2-isopropanyl-6,8-dimethoxyanthraquinone gives a reddish-orange color; rufoolivacin A, C, and D are red color while leuocorufoolivacin; Verbindung Cr11; and Verbindung Cr60 have the same yellow color isolated from *C. purpurascens*. All of these compounds were tested for their antioxidants, and leuocorufoolivacin showed the best antioxidant with an IC_{50} of 3.88 ppm.[42] *C. purpurascens* and *C. violaceus* are not only edible but also interesting in the color of their purple fruiting bodies thus increasing appetite. The fruiting bodies of *C. violaceus* also give a purple color due to the presence of an amino acid called (R)-β-dopa.[43]

In 1987, Gill and Steglich successfully isolated the yellow color of emodin, physcion, and physicion 1-O-methyl ether from the *Dermocybe* subgenus *Cortinarius.* Some rare anthraquinones were also successfully isolated, including orange needles of fallacinol (6-O-methoxycitreorosein); the bright yellow-green of flavomannin (6,6-di-O-methyl ether), the green color of atropisomer austrocolorins A1, and powder of yellow-green B1. Thirteen species of *Cortinarius* contained emodin, physion, austrocortirubin, austrocortilutein, and torosachrysone. These chemicals were able to stop *S. aureus* with IC_{50} values ranging from 0.7 to 12 ppm. However, only emodin (IC_{50} 2.0 ppm) and physicion (IC_{50} 1.5 ppm) were able to stop *P. aeruginosa.*[44] Anthraquinone compounds also have the potential to be developed as anticancers since their structure is similar to that of anthracycline commonly used in chemotherapy extracted from bacteria.[45,46,47,48]

Pycnoporus cinnabarinus is a white root fungus, also commonly named *Cinnabar polypore,* since the color of the fruiting bodies is reddish orange. Three compounds, cinnabarin, cinnabarinic acid, and tramesanguin, were successfully isolated from *P. cinnabarinus.* In Africa, this fungus can be prepared for culinary and cosmetics purposes; it was indeed listed in the traditional pharmacopeia of Africa, but in Europe, this fungus is forbidden. Native Africans and South Americans used *Pycnoporus* to cure some skin lesions and illnesses.[49,50] Smania et al. (2003) looked into how cinnabarin killed cells and viruses. They found that up to 1000 mg/kg of cinnabarin did not hurt mice and could lower rabies virus titers by up to four times.[51]

STRYLPYRONE

Styrylpyrone compounds are commonly found in fungi, especially Basidiomycetes, although they are also found in Angiosperm and Pteridophytes. Unfortunately, the abundance of mushrooms that contain styrylpyrones is rare. Thus, the utility remains still limited. *Inonotus hispidus* (Shaggy Bracket) has been used as folk medicine in China and Europe. The Compendium of Materia Medica and Shennong's Classic of Materia Medica mentioned *I. hispidus* as Sanghuang. Local people in Northeast China used it to release dyspepsia, and in Xinjiang, it was formulated to reduce indigestion, ulcers, and cancer.[52] From *I. hispidus* two compounds have been successfully isolated, a yellow color, called hispolon and hispidin. Hispolon with the skeleton structure styrylpyrone showed anti-virus and immunomodulator activities. Styrylpyrone can be extracted using polar or semi-polar solvents such as ethanol and ethyl acetate.[53,54]

There are abundant pigment derivates of styrylpyrone in fungi from Hymenochaetaceae mostly from the genera *Phellinus* and *Inonotus.* Interestingly, compounds with a styrylpyrone structure are also present in primitive plants such as Zingiberaceae, Ranulaceae, Annonaceae, Lauraceae, and Piperaceae to build an immune system against bacteria and wounds. In fungi, styrylpyrone is derived from phenylalanine amino acids, which have many functions against predators, molecular signaling, and pigmentation. Pigment derivative styrylpyrone in fungi might have a similar function as flavonoids in plants.[55]

AZULENES

Azulenes mean blue since the name azul originally comes from the Arabic "azur" and Spanish "azul." Both Arabic and Spanish mean blue color. On the other hand, naphthalene, which is the isomer of azulene, has no color or is colorless.[56] Azulene contains isoprene moiety with its derivatives, including guaiazulene and chamazulene. Both of them belong to sesquiterpene. Therefore, Tala et al. (2017) and Patino et al. (2017) used polar solvents to extract azulene, such as ethanol or methanol, followed by a purification step based on molecular weight separation like Sephadex LH-20. The blue color comes from azulene compounds isolated from *L. indigo*, which are usually used for culinary purposes, while *L. delicious* contains orange isomer gum. The compounds of 15-Hydroxy-3,6-dihydrolactarazulene and 15-hydroxy-6,7-dihydrolactarazulene also contain purple solid 7-isopropenyl-4-methyl-azulene-1-carboxylic acid.[57] Azulene and its derivatives are also developed for many applications especially solar cells, components of optoelectronics, and sensors.[58]

Lactarius indigo commonly forms symbioses with plants or trees thus being classified as ectomycorrhiza mostly in pine trees. Ectomycorrhiza is a mutual relationship between fungi and trees. The mycelium of the fungi interacts with the root of the tree then both become partners. There are so many benefits for plants or trees in the presence of ectomycorrhizal fungi. Ectomycorrhizal fungi can revive plants and trees that have suffered damage from fire, corrosion, or heavy metals. Ectomycorrhizal fungi can also repair the fertility of the soil due to flooding, soil erosion, and clearcutting. Ectomycorrhiza could prevent corrosion because it can add roots to the tree thus making the tree stronger. All fungi can absorb and digest heavy metals thus ectomycorrhizal fungi could hinder heavy metals from sticking to the root. The ectomycorrhizal fungi themselves can live from the plants or trees because of the carbon they provide to their lives.[59]

Peet et al. (2016) made 18 different kinds of azulene structural derivatives and tested them against HIV-1 on virus-like particles, TZM-BL cell lines, and infectious HIV-1 in U2OS. The findings showed that 2-hydroxyazulenes stopped the replication of the HIV-1 virus (IC_{50} 2–10 µM) and stopped HIV-1 from infecting other people (IC_{50} 8–20 µM). These results suggested that the derivatives of azulene could be developed as HIV antiretroviral candidates.[61] Another species of *Lactarius*, which is also colorful and interesting to explore is *L. lilacinus*. There are lilacinone derivatives of aminobenzoquinone in the fruiting bodies of *L. lilacinus* that give the plant its red color and blennione, a green color, that comes from *L. blennius.*[62]

PTERIDINES

The word of pteridines in Greek means wing (pteron) since it was first discovered in the wings of butterfly. Pteridines are heterocycles consisting of fused pyrazine and pyrimidine rings. Based on its structure, pteridines are classified into lumazines and pterins.[63,64] Probably the most popular compounds with pterin structures are riboflavin (vitamin B_2) and folic acid (vitamin B_9). Riboflavin, a yellow color, was successfully isolated from *R. xerampelina* but it will degrade into lumichrom if exposed to light. An analog of lumichrom that is also photoactive is 3N-methyl riboflavin isolated from *Panellus serotinus* and lampteroflavin from *Omphalotus japonicus.*[66,67] In the 1950s, methotrexate, a pteridines derivatives that is also an antifolate medicine, was usually used to treat tumors. The characteristic of pterin compounds is heterocyclic with low molecular weight. Folates are also called conjugated pterins because the structure contains a para-aminobenzoilglutamine moiety.[65]

The first lumazine was isolated from Basidiomycetes, 1-(5-amino-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl) amino-1-deoxy-D-ribitol was added. A blue-violet fluorescence of 1-deoxy-1-(6-methyl-2,4,7-trioxo-1,2,3,4,7,8-

hexahyropteridine-8-yl)-D-ribitol and 1-deoxy-1-(2,4,7-trioxo-1,2,3,4,7,8-hexahydropteridin-8-yl)-D-ribitol were first isolated from higher fungi. *Russula* sp. also has russupteridine-yellow I, II, IV, and V.[68] In 1969, Gluchoff successfully isolated three russularhodines with a red color, three russula cyanines with a blue color, and seven russula xanthines with a yellow color. The abundance of lumazines in nature is less than that of pterins thus their pharmacological activities are still undiscovered.[69,70]

Lactarius and *Russula* genera are members of the same order and family, which are Russulales and Russulaceae. The microscope examination of their spores is similar but can still be distinguished easily by a morphology test. A specific and unique feature of *Lactarius* is the presence of latex usually white milk this is called a milky cap if their fruiting bodies are squeezed while *Russula* produces no latex. A yellow-orange gum, ochroleucins A_1, isolated from *Russula ochroleuca* and *R. viscida,* will turn red if reacted with base. Sontag et al. (2006) and Clericuzio et al. (2008) used EtOAc or dichloromethane or hexane to extract pigments from Russula.[71,72]

CONCLUSION

Based on the review results obtained, natural colors are very promising for application in human health, due to their active compounds potency as anticancer, anti-HIV, antioxidant, and antimicrobial. In addition, pigments containing azulene structures from mushrooms are developed as solar cells and UV protection. However, further research needs to be done in this regard.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to this work.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

There is no conflict of interest.

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