Natural hydroquinones' antioxidant activity

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Martin T. Natural hydroquinones' antioxidant activity. J Exp Clin Microbiol. 2022; 6(3):29-32.

ABSTRACT

Despite the original simplicity of its structure, secondary metabolites generated from hydroquinone are extremely rare in nature, especially when compared to other derivatives with which it shares metabolic pathways. Its existence in a prenylated form, however, is significant, particularly in the marine environment, where it is found in a variety of algae and crustaceans. More complicated compounds, such as polycyclic diterpenes with an abietane skeleton, have been discovered on occasion. The presence of the dihydroxy group in the para position confers antioxidant potential in all cases, as it transforms into para-quinones. Natural hydroquinones with antioxidant activities that have been mentioned in the last fifteen years are the topic of this review. Through interactions with enzymes, transcription factors, and other proteins, this activity, which has been demonstrated in vitro, should lead to relevant pharmacological properties, which may be particularly relevant for the prevention of degenerative diseases of the central nervous system, as well as cancer, metabolic, and immune diseases. In conclusion, despite the fact that only a small number of compounds are known as active principles in established medicinal plants, this research has updated the pharmacological potential of hydroquinone derivatives. The following are the highlights of this review: Due to their agonistic interaction with LXR, research on sesquiterpenoid zonarol and analogues (aromatic ene-ynes) in the pharmacology of atherosclerosis is of great value; and prenylhydroquinones with a selective effect on tyrosine nitration or protein carbonylation may be of interest in the control of post-translational protein carbonylation.

Key Words: *Alkyl phenolics; Antioxidant; Hydroquinones; Marine natural Products; Meroterpenoid*

INTRODUCTION

Hydroquinone (1,4-dihydroxybenzene) is a fairly simple phenolic compound found in secondary plant metabolites in Ericales, Lamiales, and Asterales, with Ericales, Lamiales, and Asterales being the most prominent taxa. Brown and green algae, bacteria, and a large number of marine invertebrate creatures, such as sponges, cnidaria, and ascidians, all include similar chemicals. Although an in-depth examination of the biosynthetic origins of hydroquinones is beyond the scope of this article, a few broad points are worth mentioning. The p-dihydroxybenzene ring is derived from the shikimate pathway, which involves the conversion of chorismate to P-Hydroxyl Benzoate (PHB) by the action of chorismate lyase, followed by the transformation of PHB-1-hydroxylase into hydroquinone by PHB-1-hydroxylase, as detailed in the process of heterologous production of arbutin, also known as arbutoside (4-hydroxyphenyl-1-O- Alternative, less common pathways, such as the transformation of homogentisate into gentisate and the decarboxylation of gentisate into hydroquinone, are found in sponge prenylhydroquinones. Second, many natural hydroquinones contain a terpenoid component that can be rather large, which is why they are classified as part of the complicated group of meroterpenoids. In most circumstances, the aromatic ring is integrated into these types of molecules via a simple conjunction mediated by prenyl transferases, but in other cases, the ring is a part of the terpenoid skeleton and thus the benzene ring is formed via

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Received: 1-Mar-2022, Manuscript No. Puljecm-4470; Editor assigned: 3-Mar-2022, PreQC No. Puljecm-4470(PQ); Reviewed: 17-Mar-2022, QC No. Puljecm-4470(Q); Revised: 19-Mar-2022, Manuscript No. Puljecm-4470(R); Published: 26-Mar-2022, DOI:10.37532/ Puljecm.2022.6(3).29-32.

cyclic dehydrogenations. When both hydroxyls are free, hydroquinone derivatives rapidly convert into p-quinones in the presence of oxygen or metal cations. The participation of 2H + and 2e in the transition between the phenolic (reduced) and quinonic (oxidised) forms is important, and the redox potential of the process is strongly controlled by the pH of the medium and the type of the solvent. The production of an intermediate semiquinone, a molecule endowed with a certain potential to generate reactive oxygen species (ROS), which is very relevant to prospective cellular toxicity, is crucial to note for the purposes of biological activity. Since the operation of complexes I and III of the respiratory chain is based on this reaction, manifested by the pair ubiquinone ubiquinol (coenzyme Q), as reported by Frederick Crane, this concept has been crucial in the study of mitochondrial biochemistry for decades. The current review attempts to systematise studies on the antioxidant properties of natural hydroquinones based on this set of principles by assessing the most important publications published between 2005 and 2020, with some temporal extension where applicable. The analytical methodology used to study oxidative processes and the chemical structure of the active principles is used to organize this manuscript [1-4].

Free Radical Scavenging and Related Antioxidant Chemical Analysis: Hydroquinones are simple hydroquinones. Rhodiola sacra (Prain ex Raym.-Hamet) S.H. Fu (Crassulaceae) was one of the most active species in a study on the oxygen free radical scavenging properties of 70 Chinese medicinal plants, along with other species from the well-known genera Areca, Juglans, Paeonia, and Psychotria. Hydroquinone had a modest activity as a scavenger of the superoxide anion (O2) formed by a hypoxanthine/xanthine oxidase system, as assessed by spin trapping with 5,5-dimethylpyrroline-N-oxide (IC50 72 M) in further investigation on the principles of R. sacra roots. Furthermore, some other common catechins and phenolic acids, as well as the cyanogenic glycoside heterodendrin, play a role in this action, which was shown in both methanolic and aqueous extracts of the crude medication. The factors responsible for the antioxidant action of the R. sacra root extracts appear to be gallic acid and its catechin esters, based on their IC50 values of 1.5-4.0 M. The aerial portions of Origanum majorana L. (Lamiaceae) were extracted for 2 hours in boiling water, and then fractionated with hexane and ethyl acetate. The phenolic chemicals hydroquinone, arbutin, rosmarinic acid, 5,6,30 -trihydroxy-7,8,40 -trimethoxyflavone, and 5,7,30 -trihydroxy-40 -methoxyflavanone were isolated and identified from the ethyl acetate extract (hesperetin). Two free radical scavenging experiments were used to measure the antioxidant activity: With potassium ferricyanide, the 1-diphenyl-2-picrylhydrazylradical (DPPH•) assay and 2,20 -azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) radical cation (ABTS•+), as well as the Ferric Reducing Antioxidant Power (FRAP) assay. Hydroquinone (0.054% of plant dry weight) was the most effective of these chemicals in both experiments, whereas its glucoside, arbutin (0.039% of plant dry weight), was the least potent. However, as compared to the rest, both hydroquinonic principles had the strongest anti-proliferative activity on tumoral C-6 cells. Some comparisons may be extremely beneficial in order to acquire a proper idea of the relative influence of the distinct phenolic principles on the effects of O. majoring as a whole: Hydroquinone had an IC50 of 17.44 M in the DPPH assay, while hesperetin (3.81% of plant dry weight) had an IC50 of 21.44 M. Based on these findings, this last flavonoid's contribution to plant activity as a free radical scavenger agent should be roughly 20 times that of hydroquinone. Dong et al. isolated fourteen phenolics from the aerial portions of Mikania micrantha Kunth (Compositae), including hydroquinone and benzyl 5-O-D-glucopyranosyl-2,5-dihydroxybenzoate, a novel hydroquinone derivative. In ABTS•+ and DPPH• radical scavenging experiments, as well as the FRAP assay, both compounds were investigated as potential antioxidant principles, with L-ascorbic acid serving as a control. The glucoside had the greatest scavenger concentration 50% (SC50) of 0.31 M when evaluated on the ABTS assay, outperforming hydroquinone (SC50 4.57 M) and ascorbic acid (SC50 10.45 M) among the substances examined. It also showed promising efficacy in the FRAP experiment, with a reducing capacity of 0.34 mmol/g, which was significantly higher than that of hydroquinone (8.77 mmol/g) and ascorbic acid (11.32 mmol/g). In the DPPH test (SC50 > 100 M), however, the glycoside had no effect, although hydroquinone (SC50 31.96 M) demonstrated a potency similar to that of ascorbic acid (SC50 39.48 M). The authors suggested that this substance be used in future studies on chronic disorders like atherosclerosis, angiocardiopathy, and cancer that are linked to free radicals and Reactive Oxygen Species (ROS). Hydroquinone and a glycoside of the flavone apigenin were described as the most potent antioxidants in a detailed study of the phenolic components of both raw and bee-processed maize pollen taken from colonies in the province of Nan (Thailand). However, the nuclear magnetic resonance spectroscopic data that could support the identification of hydroquinone are equivocal; therefore the existence of this molecule in the examined extracts appears to be false. The hydroquinone trisaccharide 4-hydroxyphenyl-D-glucopyranosyl-(16)-Dglucopyranosyl-(16)-Dglucopyranoside was isolated as a minor from wheat germs, along with some other closely related hydroxybenzene glycosides *(Triticum aestivum L., Poaceae)* [5].

The Trolox Equivalent Antioxidant Capacity (TEAC) test, which involves oxidising ABTS to generate the free radical ABTS•+, revealed that compound's activity. In contrast to 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, the capture of ABTS•+ was evaluated (Trolox). The hydroquinone triglucoside had a slowly rising effect over 5 minutes under these conditions, with potency 1.12 times that of Trolox. The authors were able to explain how an increase in the amount of sugars in simple hydroquinones decreased the antioxidant activity in the DPPH scavenging test in earlier works. This finding, which does not occur with ABTS•+, is most likely related to the steric barrier that affects DPPH radical. Hydroquinone and its 600-O-caffeoylglucoside (robustaside B) were discovered in the leaves of Cnestis ferruginea Vahl ex DC. (Connaraceae), a laxative and antibacterial plant native to western tropical Africa. When rat mitochondria were treated with Fe2+/ascorbate to promote membrane lipid peroxidation, both phenolic principles were found to be antioxidants. There was no concentration–response association at the concentrations examined (0.05-1.0 mM), because the percentages of inhibition of the generation of thiobarbituric acid reactive species (TBARS) only ranged from 81.0 to 86.5. It is obvious that some experiments in the M, if not NM, range would have been beneficial. Furthermore, hydroquinone and robust aside B induced the permeability transition pore in the rat liver mitochondria to open, but they had the reverse effect when the opening was triggered by a rise in calcium. Release of calcium causes dysregulation of membrane function, mitochondrial enlargement, and cell death, which is consistent with the latter result. Hydroquinones Terpenoid Three compounds were identified as simple hydroquinone glycosides: arbutin, seguinoside B, and osmantolide, and three more as monoterpenoid hydroquinone glycosides: thymoquinol-2-O—D-glucopyranoside and thymoquinol-5-O—D-glucopyranoside from the aerial parts of Origanum dubium Boiss (Lamiaceae) collected in Cyprus The most active molecule in the DPPH test appears to be osmantolide, which inhibited 63% and 65% at 20 and 60 minutes, respectively, at 0.1 mM, whereas the other compounds tested did not reach 30% at identical concentrations. The authors employed 2, 20 -azobis(2-amidinopropane) (ABAP) as a free radical initiator and Trolox as a standard to inhibit linoleic acid peroxidation. The authors submitted some experimental data on potential anti-inflammatory action, but no inflammation tests were performed. Yamaguchi et al. isolated and identified the new 1-O-methyl-2-[(20E)-diprenyl]- hydroquinone from the fruits of Piper crassinervium Knuth, as well as the known (20E)-10 -oxo-diprenylhydroquinone and (20Z)- 1 0 -oxo-diprenylhydroquinone (Piperaceae). They tested these geranyl-hydroquinone derivatives' antioxidant potential by looking at their ability to suppress both DPPH• radical scavenging and luminol chemiluminescence generated by ABAP as a peroxyl radical source. In phosphatidylcholine liposomes, their protective properties against lipid peroxidation caused by Fe3+/EDTA and ascorbic acid were tested. In the DPPH assay, these prenylated hydroquinones showed significant radical scavenging abilities. Tests for lipid peroxidation, chemiluminescence, and chemiluminescence the new natural chemical had a higher lipid peroxidation potency (IC50 14.5 M) than the known compounds (6.2 and 6.3, with IC50 26.4M and 63.1 M, respectively), but was less potent than Trolox (IC50 2.6 M). The E isomer was more effective than the Z isomer among these last hydroquinones, owing to its greater liposome insertion. Hydroquinones and similar chemicals can also be found in algae. Fish et al. identified fourteen meroterpenoids from Cystoseira crinita Duby, a brown alga (Sargassaceae). There were eight novel prenyl-toluquinols, a type of methylhydroquinone chemicals, with six tetraprenyl derivatives and two triprenyl derivatives among them In addition; some other known, related compounds were discovered. In the DPPH and TBARS experiments, all of these substances were evaluated for their antioxidant capabilities. The hydroquinone derivatives had the best radical-scavenging effects in the DPPH test, with percentages of scavenging activities ranging from 93% to 97%, equivalent to -tocopherol (95%), all at 230 M. Only three compounds demonstrated notable activity at lower concentrations, with scavenging activities of 80 percent at 58 M and 30% at 23 M. All hydroquinones had similar effects to the control in the TBARS assay of peroxidation of linolenic acid methyl ester, with 69% for Butylated Hydroxyl Toluene (BHT) and 73% for -tocopherol. They showed activity between 13% and 59% those of -tocopherol in the TEAC test. The highest values in the photochemilum inescence test were 41% and 112% for -tocopherol, indicating that several of these chemicals showed significant radical-scavenging potential. Despite the large number and variety of compounds studied, neither the influence of radicals nor other structural activity correlations could be established; thus, the only chemical group of interest as an antioxidant was determined to be hydroquinone. Kamagai et al. discovered relevant activity of the methanol extract of the brown alga Dictyopteris undulata Holmes (Dictyotaceae) on the DPPH test in a screening for anti-oxidative compounds. They recovered five sesquiterpenoids, three of which are hydroquinone derivatives: isozonarol, isozonarone, and chromazonarol, after a bioassay-guided fractionation. These compounds were examined using the same technique, and the authors discovered that isozonarol had the highest DPPH radical scavenging activity, with an EC50 of 71 M, which was similar to that of the positive control, -tocopherol. Isozonarone and chromazonarol had inhibition levels of 145% and 121% respectively. Hydroquinone is clearly the active centre in this situation, with effective ROS scavenging characteristics .When the p-hydroquinone structure is removed or inhibited by other radicals, the relevant action is lost. Other isolated sesquiterpenoids were found to be devoid of action because their molecules lacked the hydroquinone core. The latter chemical was not examined in the DPPH test, but it was evaluated for its possible neuroprotective effects via the nuclear factor-erythroid 2-related factor 2 antioxidant responsive element (Nrf2/ARE) pathways. Through stimulation of the Nrf2/ARE pathway, zonarol protected HT22 hippocampal neuronal cells against oxidative stress. Because the hydroquinone group can be oxidized to a Quinone, this chemical can be called a pro-electrophilic medication. The researchers concluded that zonarol could be used as a lead medication to treat chronic neurodegenerative disorders caused by oxidative stress and mitochondrial dysfunction [6-8].

CONCLUSION

The latter chemical was investigated for its potential neuroprotective benefits via the nuclear factor-erythroid 2-related factor 2 antioxidantresponsive elements (Nrf2/ARE) pathway, rather than the DPPH test. Zonarol protected HT22 hippocampal neuronal cells from oxidative stress by stimulating the Nrf2/ARE pathway. This chemical is classified as a pro-electrophilic medicine because the hydroquinone group can be oxidised to a quinone. The researchers came to the conclusion that zonarol could be employed as a first-line treatment for chronic neurodegenerative diseases caused by oxidative stress and mitochondrial malfunction. However, in the literature reviewed, some lines of pharmacological development are plainly discernible. The neuroprotective effect of zonarol and analogues from Dictyopteris, for instance, is dependent on the stimulation of the Nrf2/ARE pathway. Furthermore, the distinctive chemistry of aromatic ene-ynes pestaloquinol analogues, as well as their agonistic interaction with LXR, proven to be quite useful for screening in atherosclerosis pharmacology. Finally, separating indiscriminate antioxidant activity from selective effects on tyrosine nitration or protein carbonylation, as occurs in Phagnalon's principles, opens up new possibilities in the control of post-translational protein modification, which is frequently seen in chronic inflammatory diseases.

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