# Review of Chemical Characteristics of An Antioxidant Compound and Biological Activity Important for Utilization in Pharmaceuticals

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**Submission date:** 05-Sep-2019 04:47PM (UTC-0700)
**Submission ID:** 1167866603
**File name:** ARTIKEL_JTPC_2019.pdf (192.73K)
**Word count:** 4691
**Character count:** 26624

# Review of Chemical Characteristics of An Antioxidant Compound and Biological Activity Important for Utilization in Pharmaceuticals

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**ABSTRAK**

Chemical characteristics of a compound to be an antioxidant compound are more reactive than the compounds making up cells and tissues as well as metabolic component compounds, to radical compounds in the mammalian metabolic system. A highly reactive compound is (1) has one or more unpaired electrons in the form of radical electrons or compounds that lose or excess electrons form ionic (2) have many paired electrons (3) the distance between groups or atoms that have radical electrons very close or distance between same ion in a compound or the distance between groups or atoms which have electron pairs very close in term chemical bond or in space or conformation (4) and compounds that contain a lot of oxygen atoms. Therefore, a group of potential compounds that have strong antioxidant activity is phenolic, especially polyphenols because they have a hydroxy group or another group that has many paired electrons, located in an aromatic ring very close in chemical bonds, or an electron pair between aromatic rings in a very close compound based on space. Furthermore, highly reactive compounds are potentially toxic because they react easily with chemical compounds making up cells and tissues, as well as metabolic component compounds; such as proteins, lipids as fats, carbohydrates, non-fat lipid compounds, and nucleic acids (DNA and RNA). Therefore, the excess of antioxidant compounds in the metabolic system is not good, if there is no free radical in the metabolic system or excessive radical compounds. Thus, the biological activity of antioxidant compounds that must be known if an antioxidant compound will be used in the pharmaceutical field is toxicity. Toxicity information that prospects to be continued as a pharmaceutical antioxidant product is minimally sourced from preclinical testing

*Keywords: Antioxidants, Chemical Characteristics, Biological Activity, and pharmaceutical potential*.

# I. INTRODUCTION

The most chemical reaction in the biological metabolism system (animals, plants, humans) is oxidation, which produces several oxide compounds including oxidants, hydroxy, and various other reactive oxide compounds (Frankel et al., 1983). These oxide compounds would have one or more unpaired electrons or excess or lack of electrons to form ionic, or have a lot of oxygen so that it is very reactive, which is also reactive to the chemical compounds that making up cells and tissues, and also to biological metabolism components such as enzymes and non-enzymes, as well as against various other metabolites. Oxide compounds that have one or more unpaired electrons as a result of oxidation reactions in the metabolic system are called endogenous oxygen radical compounds (Halliwell dan Gutteridge, 1991). The oxygen radical compounds react immediately with other endogenous reactive chemical species in metabolic processes including those with a special role to react with oxide radical compounds. Reactive endogenous compounds with special utility to react with these radical oxides called endogenous antioxidants (Sichel et al., 1991). Oxide radical compounds that formed in metabolism are normal conditions in the process of metabolism (anabolism and catabolism) and there are reactive compounds in the metabolic system that have the special role of reacting with various radical compounds that are formed, so that these radical compounds do not react with the cell constituent compounds and tissue and component compounds in the metabolic system. Endogenous radical compounds become a problem if there is an increase in the number of metabolic systems. Excess types and the number of radical compounds in the metabolic system compared to the amount of endogenous antioxidants, potentially increasing the reaction of these radical compounds with metabolites in cells, such as proteins in the form of enzymes and non-enzymes, lipid compounds, hormones, to nucleic acids (Breen and Murphy, 1995). Therefore, free radical compounds are claimed to be one of the causes of degenerative diseases. Radical compounds are not only radical oxides, but also non-oxygen compounds can be formed radical compounds that are also very reactive as well as radical oxide compounds. The amount and type of oxide and non-oxide radical compounds that exceed normal conditions are called free radical compounds because they can freely react with chemical species that exist in the metabolic system, because of their high reactivity. Thus, the very main chemical characteristics of a compound to become an antioxidant compound, must be more reactive to free radical compounds compared to the compounds making up cells and tissues as well as to the chemical compounds of metabolic components.

The term antioxidant as if a compound that is only reactive to oxygen radicals, but the true meaning is compound is reactive to all radical compounds, while oxidants are one of a number of these radical compounds. The term oxidant by some people is interpreted as an oxide compound or compound that contains oxygen, and this is the most compound in the metabolic system, so it is considered as an oxidant. Oxidants are oxygen radicals with the symbol **O.** Oxidants are oxygen radicals with the symbol **O.** representing all chemical compounds that have unpaired electrons called radical compounds. Oxygen radicals with the symbol **O.** are generally in the form of **.O2** molecules or in the form of reactive oxygen compounds. If there are other compounds that easily react with radical compounds, they must be called antioxidants, even though the oxidant in question is not oxygen radicals, but other non-oxygen radical compounds. The term antioxidant is finally widespread in society both in educated societies especially those who are not educated still call it an antioxidant, if the compound has a higher reactivity than surrounding chemical compounds.

The term antioxidant arises because the most reaction in the metabolic system is oxidation which produces several oxygen radicals that are very reactive and act as intermediates for further reactions. If a compound is easy to react with oxygen radicals or reactive oxygen compounds are called antioxidants, so if a compound is easy to react with non-oxidant radical compounds or non-reactive oxygen compounds still called antioxidants, and chemically should be called anti-radical compounds. Radical compounds, such as oxygen radicals, reactive oxygen compounds, non-oxygen radical compounds and non-reactive oxygen compounds will be formed in every reaction process, especially reactions that require catalysts.

Metabolism, for example, a chemical reaction forming or decomposing metabolites in living cells is a chemical reaction that takes place in several stages so that it requires time or chemical kinetics that is complicated and long time. A metabolic reaction is an enzymatic reaction, even using a number of enzymes to poly-enzymes for the metabolic processes of both anabolism and catabolism. In this process certain radical compounds and reactive compounds are formed which are dominated by oxygen radicals and reactive oxygen compounds. Metabolic reactions often occur excess radical compounds, but there are anti-endogenous radical compounds in the form of enzymes and non-enzymes. Therefore, the excess of radical compounds metabolically does not cause problems. The excess of radical compounds in the metabolic system is caused more by exogenous inflation in the form of chemical compounds, extreme weather to psychological (Clopton and Saltman, 1995). Because it is needed anti-radical compounds or exogenous antioxidants both synthetic compounds and natural product compounds, especially from biological. Antioxidant researchers focus more on natural product compounds with primitive thinking that natural compounds are considered harmless.

Characteristics of antioxidant compounds that are more reactive compared to cell constituent compounds and metabolic component compounds sufficiently illustrate that excess antioxidant compounds in cells or tissues will be bad because antioxidant compounds are very reactive so that they can react with various cell constituent compounds or metabolic compound components, because in the metabolic system there are no endogenous radical compounds.

Probing or exploring for antioxidant compounds, which are generally conducted by researchers, are in vitro using synthetic radical compounds as reagents of radical compounds such as 1,1 - diphenyl-2-picrylhydrazyl (DPPH); 2,2-Azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and so on. Chemically, the evaluation of a reactive compound can be done based on observing the structure's form, namely the relationship between the structure of the compound with reactivity or the tendency to react easily. Observation of the structure of compounds is also useful for determining the stability of these compounds against various environmental disturbances, even structural observations of chemical compounds are also useful for predicting the type of biological activity possessed by these compounds. The review of this article is to reveal some chemical characteristics of a potential compound as an antioxidant compound. Antioxidant activity that is required in the pharmaceutical field is its ability to react with radical compounds in cells and tissues including radical oxygen and reactive oxygen compounds, compared to the ability of cell constituent compounds and / or metabolic component compounds or all metabolite compounds to react with radical compounds either endogenous radicals and exogenous. However, if the antioxidant compound is a reactive compound, then the potential for reactions with cell and tissue constituent compounds and metabolic chemical components. If this reaction occurs, the antioxidant compound is also potentially toxic.

## II. METHOD

The focus of this article is a review of the literature study approach of a number of scientific articles from research results and reference books which are also a collection of various research results. The literature review method uses comprehensive to synthetic analysis with chemical and pharmaceutical scientific approaches related to the assessment. The purpose of the study is to display the physicochemical properties of a compound that is characteristic of being an antioxidant compound and the biological activity criteria that accompany the antioxidant activity as a condition to be utilized in the pharmaceutical field. The data shown are (1) chemical structure characteristics of compounds which are potentially reactive to radical compounds and (2) biological activities that must be known for the purpose of their use in the pharmaceutical field. Data sources used include (I) Natural Antioxidant Exploited Commercial by Schuler, P (1990) in Husdont BJ, Foods Antioxidants: New York, Elsevier Applied Science (II) I Matteo V; Esposito E (Apr 2003), "Biochemical and therapeutic effects of antioxidants in the treatment of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis", Current Drug Targets. CNS and Neurological Disorders, 2 (2): 95–107 (III) Solomon (1993) Organic Chemistry (IV) Green GA (Dec 2008), "Review: antioxidant supplements do not reduce all-cause mortality in primary or secondary prevention" , Evidence-Based Medicine; (V) Bjelakovic G; et al. (2007). "Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis". JAMA. 297.

## III. RESULTS AND DISCUSSION

### 3.1. Oxygen Radicals and Reactive Oxygen Compounds in Mammals

The most important chemical in living things and their environment is oxygen. If water is the primary need of living things and their environment, then oxygen is a super primary need for living things and their environment. Therefore, oxygen is found in all layers of the atmosphere with levels varying up to 20% of the composition of the air. All chemical reactions that occur in living things and their environment require oxygen, except for anaerobic living things. Therefore, the most reaction in aerobic living cells and their environment is oxidation, which is the reaction between a compound and oxygen to form various new compounds including oxide compounds that are needed by living things and their environment directly or indirectly. Oxygen is in the form of gas, so it is easy to form oxygen radicals either in the form of atoms or radical oxygen elements with the symbol O. or oxygen radicals in the form of molecules with the symbol. $O_2^{\cdot-}$ or in the form of oxide compounds such as hydroxides (.OH) and other reactive oxygen compounds. Radical oxygen and reactive oxide compounds are needed by living things and their environment because it is very reactive, so it is easy to form various chemical compounds needed by living things and the environment. Thus, oxygen radicals or reactive oxide compounds are needed by living things and their environment as a reaction chain for the formation of various chemical species that are needed (Favier, 1982). Oxygen radicals and reactive oxide compounds become dangerous to living things if qualitatively and quantitatively excessive so that they react with other compounds including proteins, lipids, carbohydrates, and nucleic acids in living cells including humans (Janssen et al., 1993). Water is one of the oxidation reactions between oxygen and hydrogen molecules available in the environment and finally forms $H_2O$ or water in three forms, gas, liquid and solid, which is dependent on the environment. Likewise, $CO_2$ as a gas needed by plants for the formation of

carbohydrates and others, which is also the result of the reaction between Oxygen and Carbon molecules to form $CO_2$ gas. Likewise, a variety of other chemical reactions in the framework of the formation and decomposition of a compound that is needed.

Oxidation reactions or reactions of compounds with oxygen in the environment and in living cells occur gradually and at some stage radical oxygen is formed and / or reactive oxygen compounds. Stages of oxidation reactions produce several radical oxygen and reactive oxide compounds to accelerate the formation of compounds needed and to decompose a compound that is not needed in the reaction process. Thus, oxygen radicals are needed by a chemical process that occurs in the environment and in living things. Oxidation reactions in aerobic living things begin from a respiratory event, which is the process of taking oxygen in the environment needed for the oxidation reaction in the cells and tissues of these living things. The formation of oxygen radicals and reactive oxide compounds in cells and tissues occurs endogenously and exogenously. Endogenous reaction is a normal metabolic process with complex reaction stages and at that stage various oxygen radicals or reactive oxide compounds are formed as intermediate compounds or as intermediate compounds and immediately react with other species to form metabolites or decompose a metabolite in accordance with the metabolic objectives. Furthermore, exogenous radical formation is caused by the infusion of a compound which is easy to form oxygen radicals or reactive oxide compounds; such as certain pesticide infections such as Carbon tetrachloride ($CCl_4$); benzopyrene resulting from grilling of fatty meat, food additives carminic acid, and others (Elstner, 1991). Some of the reactions of oxygen radical formation and reactive oxide compounds that occur in cells and tissues as metabolic events are:

$$2NADH + H^+ \longrightarrow 2\,NAD^+ + H2O + Energy$$

$$ADP + Energy \longrightarrow ATP$$

The reaction is the formation of energy normally in the mitochondria through oxidative phosphorylation. The reaction may not take place completely so that reactive oxygen compounds are formed, for example:

$$O_2 + e \longrightarrow .O_2^-$$

$$O_2 + e + H^+ \longrightarrow \cdot COOH$$

$$O_2 + 2e + 2H^+ \longrightarrow H_2O_2$$

$$O_2 + 3e + 3H^+ \longrightarrow \cdot OH + H_2O$$

$$O_2 + 4e + 4H^+ \longrightarrow H_2O_2$$

The results of these reactions produce superoxide ion radicals, peroxyl radicals, hydrogen peroxide, and hydroxyl radicals. Because of that the term antioxidant can be understood, because in general the compounds needed to react with several radical oxygen and reactive oxygen compounds. The reaction is an endogenous or normal event in the metabolic system. Radical Superoxide Ion ($.O_2^-$) is very reactive and is produced in several places such as mitochondria, chloroplasts, microsomes, glycosomes, peroxisomes, and cytosols (Elstner, 1991). The formation of superoxide ions occurs through several mechanisms such as a side reaction involving $Fe^{++}$ ions in the oxidative phosphorylation process, hemoglobin oxygenation, hydroxylation of the monooxygenase enzyme in cytochrome P450 and cytochrome b4; reactions in mitochondria and granulocytes catalyzed by NADH/NADPH oxidase; a

reaction catalyzed by Xanthine Oxidase (XO) in which Xanthine can produce uric acid which acts as a non-enzyme antioxidant. Following is the reaction:

$$XH + H_2O + 2O_2 \longrightarrow X\text{-}OH + 2O_2^{\cdot -} + 2H^+$$

Xanthin ⟶ Uric Acid

Under normal circumstances, mammalian cells do not have the xanthine oxidase enzyme, but this enzyme is derived from the xanthine dehydrogenase (XD) enzyme that catalyzes the following reactions:

$$XH + NAD^+ \; H_2O \xrightarrow{XD} X\text{-}OH + NADH + H^+$$

The xanthine dehydrogenase (XH) enzyme undergoes proteolysis and changes to xanthine oxidase (XO) when hypoxia or ischemia occurs, namely:

$$XD \longrightarrow XO + \text{Peptide}$$

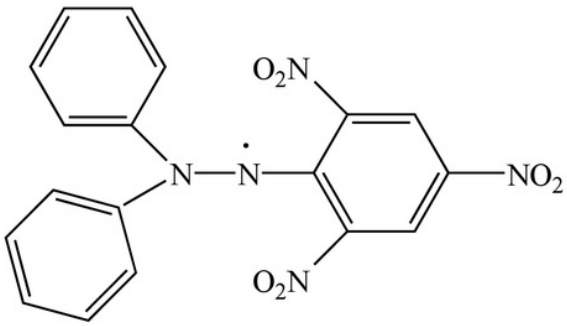
Changes of xanthine dehydrogenase to xanthine oxidase is irreversible, when a normal oxygen supply will form a highly reactive superoxide compound, which can damage the tissue if endogenous antioxidants are not available. There are still oxygen radicals and reactive oxygen compounds formed in mammalian cells, such as peroxyl radicals (.OOH), hydrogen peroxide ($H_2O_2$); hydrogen hydroxyl radical (.OH); singlet oxygen ($^1O_2$) which is very reactive compared to others. The site of formation of various oxygen radicals and reactive oxygen compounds is chloroplasts, mitochondria, endoplasmic reticulum, microbodies, plasma membranes, cell walls, and others.

The results of this brief discussion show that oxygen radicals and reactive oxygen compounds that threaten cell damage and metabolic systems so that the chemical compounds used to check the damage are called antioxidants. Thus, the search for antioxidant compounds must estimate the reactivity of these potential antioxidant compounds with the chemical structure of oxygen radicals and reactive oxygen compounds. In addition, the antioxidant compounds which are also quite reactive compared to the cell and tissue constituent compounds and the metabolic constituent compounds also threaten the reaction with the cell constituent compounds.

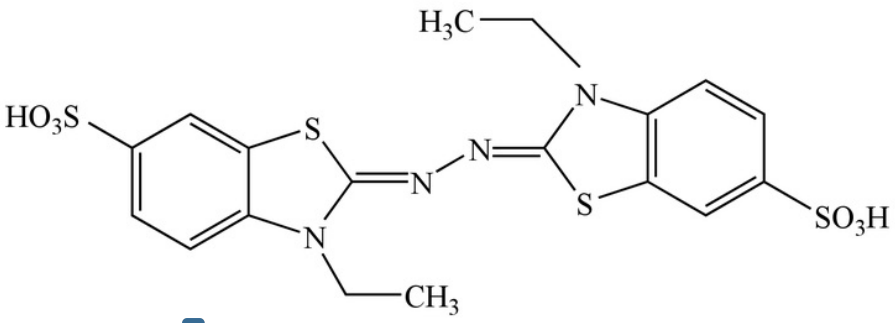
### 3.2. Chemical Characteristics of Antioxidant Compounds

The role of antioxidant compounds is as a reagent of free radical compounds found in mammalian cells and tissues and in the environment. If antioxidant compounds are used as reactive reagents for radical compounds in mammalian cells and tissues, their usefulness is related to health, fitness, and even intelligence. This is caused by several radical compounds in cells and tissues that have the potential to react with a number of compounds making up cells and tissues, including cells related to health, fitness, and intelligence. However, this potential needs to be tested in vivo from the preclinical scale, clinical observation, to clinical trials. It has been explained that the most dominant radicals in mammalian cells and tissues are oxygen radicals and reactive oxygen compounds. Therefore, if the use of anti-radical compounds for health, fitness and intelligence purposes is called an antioxidant; because in general radical compounds in cells and tissues are oxygen radicals and reactive oxygen compounds.

Chemical characteristics of a compound has the potential as an antioxidant, if the compound is more reactive to oxygen radicals and reactive oxygen compounds as free radicals (free equal to no function), compared to its reactivity to the compounds making up cells and tissues as well as various compounds of metabolic components. Therefore, the requirements of a compound as an indicator of antioxidant testing are relatively stable radical compounds or reactive oxygen compounds. If in vitro shows the ability of a compound as a powerful antioxidant, then the compound is expected to be more reactive to oxygen radicals and reactive oxygen compounds than the constituent compounds of cells and tissues and compound components in the metabolic system. Some examples of compounds that acts as reagents in antioxidant tests are 1,1 - diphenyl-2-picrylhydrazyl (DPPH) and also compounds 2,2-Azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS). The chemical structure of the two antioxidant test compounds is shown in the following figure.




1,1,- difenil-2-pikrilhidrazil (DPPH)




2,2-Azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS)

Figure 1. The structure of DPPH and ABTS compounds an Antioxidant Test Reagent

The chemical structure of DPPH shows a radical compound that is stable enough to be isolated after synthetics. One unpaired electron as the identity of the DPPH radical compound which is located on the N atom and flanked by three stable aromatic rings has caused the radical compound to be stable compared to the general radical compound. The unpaired electrons in DPPH are not located on the O

atom, but as a radical compound will surely be reactive if present in the compound. Thus, the DPPH radical stability is not caused by having N radicals and not O; however the position of the radical atomic space is quite protected.

Furthermore, ABTS antioxidant test reagents are not radical compounds but include reactive oxygen compounds. The structure of ABTS compounds containing O, N, S, and double bonds shows that ABTS has many electrons, especially free paired electrons, namely O, N, and S atoms; and the double bond in the form of a ring will easily resonate to form an ionic and even radical. Therefore, ABTS is reactive enough to be an antioxidant test indicator compound representing a non-radical but reactive compound. Characteristics of radical compounds used as antioxidant test reagents have a Nitrogen atom that symbolizes that the reaction competitors in the metabolic system are a number of elements Nitrogen as the main symbol of protein which is a constituent of tissues, enzymes and hormones, to nucleic acids (DNA and RNA) in animals and humans. Thus, the chemical characteristics as a condition for being a good antioxidant compound are shown below.

a. The molecular structure of compounds is simpler
b. The electron affinity is quite high compared to the chemical compounds making up cells (metabolites) and chemical components in the metabolic system so that it is more reactive
c. Has a lot of resonance structure
d. Easily forms the structure of radical compounds
e. Having a group that contains lots of free electronic pairs.

Specifically, for antioxidant compounds, what is needed is reactive to oxygen radicals and reactive oxygen compounds, because various compounds are present in cells and tissues and in the metabolic system. Both radical oxygen and reactive oxygen compounds are both highly reactive, so it is easy to find various antioxidant compounds both synthetically and naturally. Chemical characteristics associated with the reactivity of compounds to other compounds are shown below in order to the right, getting weaker. The potential reactivity as an antioxidant based on its reactivity that will be more reactive compared to the chemical compounds making up cells and tissues of mammals and metabolic component compounds, namely:

*atomic oxygen radicals> atomic halogen radicals> molecular oxygen radicals (O2)> molecular halogen radicals (X2)> radical oxygen compounds> radicals non oxygen compounds and non halogens> compounds with the most free paired electrons with very close positions based on chemical bonds and conformations structure> compounds with the most paired free electrons> phenolic compounds> positive ionic elements> negative ionic elements (Solomon, et al., 1993).*

All the chemical characteristics of these compounds for antioxidants are based solely on their reactivity review of radical compounds that are considered to be intruding in cells and tissues; while toxicity related testing is needed to determine it. The natural product compounds that conform to these characteristics are the flavonoid class. The compounds from these groups can compete with chemical species in cells, both as components and metabolites involved in the metabolic system. Some classes of compounds and compounds including phenolics are simple phenol compounds, lignans, neolignanes, lignin, stilbene, naphthoquinone, anthraxone, flavonoids, anthocyanins, tannins, coumarin, chromone and xanton. The characteristic of these compounds is the aromatics which contain hydroxyl groups.

Synthetic compounds, in general, also have strong antioxidant activity, because of their simpler structure, they contain many electron pairs, so they have strong electron affinities. However, synthetic compounds are very stable or difficult to occur biodegradation so their use as antioxidants requires certainty of long-term toxicity data to avoid undesirable effects. One example of a useful synthetic

antioxidant is BHA (Butyl Hydroxy Anisole), but it is only used to prevent interference with the stability of radical compounds from the environment or as a protector of various pharmaceutical and food products.

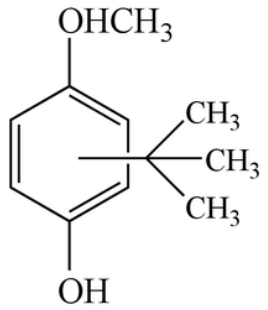



Figure 2. Synthetic Antioxidant Compounds (Butyl Hydroxy Anisol or BHA)

**3.3. Important Biological Activity Antioxidants for Pharmaceuticals**

The role of antioxidant compounds is for health and for the protection of pharmaceutical products and food from environmental oxidation. The chemical characteristics of an antioxidant compound must be more reactive to disruptive radical compounds than to the compounds making up cells and tissues and to the chemical components in the metabolic system. In testing antioxidant compounds against candidates for antioxidant compounds using chemical compounds as test reagents with indicators of the ability to react with these indicator compounds. The strength of an antioxidant is largely determined by the reactivity of a candidate compound to the antioxidant test indicator compound. The more reactive a candidate compound is, the more potential it is as an antioxidant compound. However, a reactive compound also has the potential to react with the constituent cells and tissues as well as compound components in the metabolic system. If an antioxidant compound is to be used as a pharmaceutical product for health, then the potential generated through in vitro testing cannot yet be utilized to avoid unwanted effects. If an antioxidant candidate compound can react with cell-building compounds, such as fat tissue, protein, non-fat lipid compounds, carbohydrates, to nucleic acids, the compound is toxic. Thus, biological activity that must be known to an antioxidant candidate compound is toxicity. Toxicity information is very important to anticipate the occurrence of undesirable effects.

## IV. CONCLUSSIONS AND SUGGESTIONS

Conclusions of this article are:

1. Chemical characteristics of a potential compound as an antioxidant compound for health are more reactive to a variety of oxygen radicals, reactive oxygen compounds, non-oxygen radical compounds present in cells and tissues of mammals compared to their reactivity to the chemical constituents of cells and tissues and chemical compounds of metabolic components in mammals
2. Chemical characteristics that are potential as antioxidants are atomic oxygen radicals, atomic halogen radicals, molecular oxygen radicals ($O_2$), molecular halogen radicals ($X_2$), oxygen radicals compounds, non-oxygenated oxygen compounds and non-halogen compounds, compounds with the most paired free electrons many with very close proximity based on chemical bonds and structural

conformations, compounds with the most free paired electrons, phenolic compounds, positive ionic elements, negative ionic elements

3. Biological activities that must be known to compounds that have been designated as antioxidants and which will soon be utilized in the form of pharmaceutical products, are toxicity with minimal accuracy of pre-clinical test results.

## SUGGESTIONS

1. Important knowledge for the search for antioxidant compounds is a good understanding of the chemical characteristics of compounds that have the potential to have antioxidant activity including knowledge of the relationship of the structure of compounds with their reactivity; and that knowledge is well studied in Physical Organic Chemistry
2. Compounds that are known to have strong antioxidant activity and are potentially used in pharmaceuticals, the antioxidant compounds must be tested for toxicity up to the preclinical scale, because an antioxidant compound describes reactive, and reactive compounds also have the potential to react with the constituent compounds of cells and tissues and all metabolites in the metabolic system.

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