# Chapter 6
# QSAR of Antioxidants

**Omar Deeb**
*Al-Quds University, Palestine*

**Mohammad Goodarzi**
*Katholieke Universiteit Leuven, Belgium*

## ABSTRACT

*Antioxidants are substances that protect cells from the damaging effects of oxygen radicals, which are chemicals that play a part in some diseases such as cancer and others. Antioxidants are expected to be promising drugs in the management of these diseases by removing oxidative stress. Most of the modeling approaches involved in designing new antioxidants is based on Quantitative Structure-Activity Relationship (QSAR). A number of QSAR studies have been conducted to elucidate the structural requirements of antioxidants for their activities in order to predict the potency of these compounds with regard to the targeted activity and to direct the synthesis of more potent analogues. The main focus of this chapter is on the QSAR modeling of antioxidant compounds. The authors provide different QSAR studies of antioxidant compounds and try to compare between them in terms of the best models obtained and their use in designing potential new drugs.*

## INTRODUCTION

Generally, antioxidants are defined as molecules, which are capable of slowing down the oxidation mechanism of an oxidizable compound. At the same time, oxidation represents an essential part of aerobic life and our metabolism, since oxygen is the ultimate electron acceptor. Antioxidants play a significant role in cell protection against oxidative stress. Because of the ability of antioxidants, scientific evidence suggests that these molecules reduce the risk of chronic diseases including cancer and heart disease. Primary sources of naturally occurring antioxidants are whole grains, fruits, vegetables etc.

Therefore, much attention has been devoted recently to research into the role of plant-derived antioxidants in food and human health. The beneficial influence of many foodstuffs and beverages including fruits, vegetables, tea, coffee, and cacao on human health has been recently recognized to originate from their antioxidant activity.

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In spite of the fact that there are many experimental techniques used to determine antioxidant activity of a given molecule, such techniques are not only time consuming but also costly. Alternatively, using Quantitative Structure-Activity Relationship method, one can screen a large number of compounds and check for their potency as an antioxidant. For this purpose, the most common methods used *in vitro* determination of antioxidant activity are reviewed and presented.

This chapter deals with Quantitative Structure-Activity Relationship (QSAR) of antioxidants. At first, the definition of an antioxidant is given including it's mechanism of action and methods of antioxidant determination. The issue of computer aided drug design is then discussed, focusing on the quantitative structure activity relationship (QSAR). The QSAR section starts with history and the earliest efforts made in this field, types of descriptors, statistical analysis methods from a simple linear regression such as Multiple Linear Regression (MLR) to biased regression based on Principal Component Analysis (PCA), such as Partial Least Squares (PLS) to nonlinear techniques such as Artificial Neural Networks (ANNs) and Support Vector Machines (SVMs). Moreover, a part of this chapter is devoted to the validation of QSAR models, explaining the internal and external validations. At the end, different QSAR studies of the antioxidant compounds are discussed. These QSAR models were built on different types of compounds such as Flavonoids, Hydroxyphenylureas, curcumin analogues, Hydroxybenzalacetones, Phenolic derivatives bearing NO donor groups and Coumarin derivatives. Finally, it was concluded that more attention should go to the building of QSAR models for antioxidant activities in order to design more efficient drugs with potential antioxidant activity.

## BACKGROUND

### Antioxidants

Prior to defining what an antioxidant is, we would like to use the term oxidation as a chemical reaction which transfers electrons or hydrogen from one substance to another. These oxidation reactions can produce free radicals, which are unstable molecules that lose one of their electrons and therefore become unbalanced and highly reactive. These unstable molecules can then start chain reactions in a cell and therefore, may cause damage or result in death of these cells. These free radicals are free moving compounds that travel around the body trying to become stable by taking electrons from healthy compounds. Further free radicals are formed after a successful steal, damaging healthy cells in the progression. These free radicals are the main reason behind heart disease, cancer, aging and other diseases. Therefore, an antioxidant is a substance that inhibits the oxidation of other molecules and terminates the chain reactions by removing the free radicals and inhibiting other oxidation reactions. In other words, an antioxidant is a stable molecule that donates an electron to a free radical neutralizing it and therefore, reducing its capability to damage other cells.

Antioxidants are extensively used as ingredients in dietary supplements with the hope of maintaining health and preventing diseases. At the same time, these antioxidants have many industrial uses such as preservatives in food and cosmetics, and preventing the degradation of rubber. As is known, antioxidants are abundant in fruits and vegetables. Examples of antioxidants that are formed during metabolism in the body, or endogenous antioxidants (Enzymes), are glutathione, ubiquinol, uric acid etc. Some antioxidants are present in the diet while others must be supplied in the diet such as vitamin C, vitamin E and others. In this case, they are called exogenous antioxidants and can be derived from natural sources but also can be synthesized compounds (Benzie, 2003; Knight, 1998; Matill, 1947; Sies, 1997; Valko, Leibfritz, Moncol, Cronin, Mazur & Telser, 2007; Vertuani, Angusti & Manfredini, 2004; Wolf, 2005)