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## 4-Hexylresorcinol a New Molecule for Cosmetic Application

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### Abstract

4-hexylresorcinol is the most studied and well known alkylresorcinol derivative, known for its pharmacological properties as anesthetic, antiseptic and anthelmintic. It can be both applied topically in creams and included as an active ingredient in throat lozenges. Its interest as a cosmetic ingredient is more recent and is increasing owing to its anti-oxidant, anti-glycation and melanogenic inhibitory properties and that it is safe to use. All those elements make 4-hexylresorcinol a cosmetic ingredient of choice for skin care products. This short review summarizes its mechanism of action and some evidences of its efficacy in certain biological processes of interest in skincare.

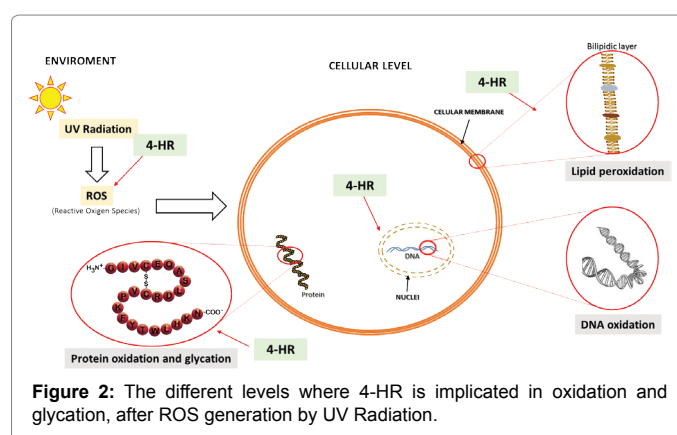
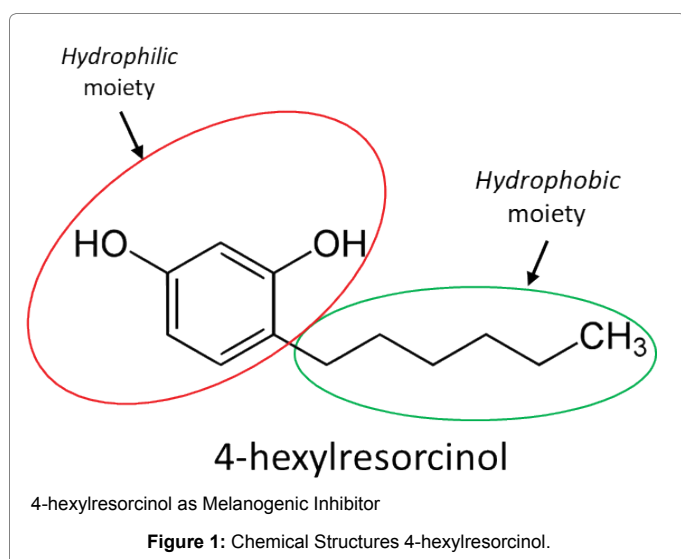
**Keywords:** 4-hexylresorcinol; Pigmentation; Photoaging; Oxidative stress; Glycation

### What is 4-hexylresorcinol?

4-hexylresorcinol (4-Hexyl-1,3-benzenediol; 4-HR) is an alkylresorcinol (AR) with 6 methylenes in length at fourth position included in the list of drugs in the World Health Organization (WHO) in 1999 (Figure 1). It is an organic amphiphilic compound that mimics the tyrosinase natural substrate, tyrosine. It is an analog of resorcinol, a compound used as an antiseptic and disinfectant in topical use [1]. It has amphiphilic properties, possessing a hydrophilic moiety and a hydrophobic moiety (highlighted in green circle in its structure Figure 2). This amphiphilic character makes 4-HR able to interact with the phospholipid bilayers of biological membranes while its hydrophilic moiety makes it possible to share a proton in aqueous media [2,3]. Furthermore, 4-HR has a GRAS (Generally Recognized as Safe) status, being considered safe and also effective as an anti-browning agent in food applications [4].

### 4-Hexylresorcinol as Melanogenic Inhibitor

The melanin synthesis is an important biological process of pigmentation of the skin. Melanogenesis is influenced by the solar radiation which increases the synthesis of melanin pigments (eumelanin and pheomelanin). The synthesis of melanin starts from the conversion of L-tyrosine into L-DOPA followed by the conversion



**Figure 2:** The different levels where 4-HR is implicated in oxidation and glycation, after ROS generation by UV Radiation.

of the latter to DOPAquinone by the tyrosinase enzyme. Tyrosinase converts L-tyrosine into L-DOPA and L-DOPA into DOPAquinone by its monophenolase and diphenolase activities, respectively. Then, a series of enzymatic reactions further convert the DOPAquinone intermediate in the different human skin melanin pigments. 4-HR resorcinol potently inhibits both monophenolase and diphenolase activities of mushroom tyrosinase [5,6]. It is thought that 4-HR binds to tyrosinase directly by competing with its natural substrate, L-tyrosine, and blocking its enzymatic activity [7]. Interestingly 4-HR was demonstrated to be more potent inhibitor of tyrosinase for both tyrosine substrates (L-tyrosine and L-DOPA) than hydroquinone, kojic acid or licorice extract (Table 1) [8-10].

### 4-Hexylresorcinol as Antioxidant

Oxidative stress in skin plays a major role in the aging process. This is true for intrinsic aging and even more for extrinsic aging. Although

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Compound	IC <sub>50</sub> (µM) Mushroom tyrosinase
4-Hexylresorcinol	1.2 [7]
Hydroquinone	26 [7]
Kojic acid	300 [8]

**Table 1:** Potency (IC<sub>50</sub>) values (µM) of 4-hexylresorcinol, hydroquinone and kojic acid on inhibiting mushroom tyrosinase activity.

the results are quite different in dermis and epidermis, extrinsic aging is driven to a large extent by oxidative stress caused by solar light including Ultraviolet (UV) Radiation. UV radiations are known to induce Reactive Oxygen Species (ROS) at the cellular level leading to cellular oxidative stress [3,11-13]. Skin cells suffering oxidative stress activates to a certain level the antioxidant machinery comprising Glutathione (GSH) that protects cells from oxidative damage as well as some primary antioxidant enzymes, such as Glutathione Peroxidase (GPX) and Glutathione Reductase (GR) [14,15]. It has been proven in DNA damage models in human lymphocytes induced by H<sub>2</sub>O<sub>2</sub> that 4-HR administration increased GSH levels but also GPX and GR activities, limiting subsequently oxidative stress and DNA damage [16]. As a phenol derivative, 4-HR, can also donate a proton to free radicals by means of its phenolic hydrogen allowing it to scavenge both peroxy radical and oxygen superoxide and reduce peroxidation of lipids [2,17,18]. Finally, reactive oxygen species may also lead to oxidation reactions of proteins [19]. Due to its amphiphilic character and hydrophilic moiety, 4-HR is able to interact with both with lipids and proteins to efficiently reduce their oxidation [2,3].

#### 4-Hexylresorcinol as a Non-Enzymatic Glycosylation Inhibitor

Glycation is considered together with oxidative stress as one of the key factors in skin aging [18]. Glycation resulting from the non-enzymatic addition of sugars to proteins generates abnormal protein cross-linking or protein adducts between adjacent proteins in the skin. Glycation leads to the formation of products called Advanced Glycation End-Products (AGEs) which can be formed either intra- or extracellularly [20]. The glycation reaction results from a non-enzymatic reaction between a sugar and a free amine group of Lysine, Arginine amino acids of proteins. Maillard reaction is one of the reactions that take place during the process of non-enzymatic glycation of proteins. 4-HR was found *in vitro* to inhibit the formation of Maillard reaction products [21]. Moreover, since glycation is linked to ROS production [22,23] antioxidant activity of 4-HR could also limit the formation of abnormal cross-linking of proteins.

#### Anti-inflammatory Effects of 4-HR

Inflammation is a complex physiological process, where the transcription factor NF-κB (Nuclear Factor-Kappa Beta) has been documented to play an important role in the inflammatory response [24,25]. NF-κB is activated by numerous pro-inflammatory stimuli. ROS triggers NF-κB, which in the canonical pathway is activated by IκB kinase (IKK) and translocate to the nuclei upregulating the expression of inflammatory mediators, such as iNOS, COX-2 and cytokines like TNF-α and IL-1β leading to inflammation [26]. Natural phenolic compounds have been considered as NF-κB inhibitors [27] and alkylresorcinols (including 4-HR) have demonstrated to have an anti-inflammatory effect [26]. Recently, 4-HR has been reported to inhibit NF-κB phosphorylation *in vitro* while in different studies, the ability of inhibiting NF-κB of 4-HR was related with an increased expression of ECM (extra cellular matrix) proteins *in vitro* in human's fibroblast, with a significant clinical improvement in photo damaged skin [28,29].

#### Conclusion

Due to its anti-oxidant, melanogenic and glycation inhibitory properties, 4-hexylresorcinol is a promising molecule for cosmetic/aesthetic application including the treatment of hyperpigmented disorder and photo-aging.

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