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The multiple biological effects of new resveratrol derivatives

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ABSTRACT: The development of new drugs is a long-term and expensive process. Among the strategies to find out new drugs, natural products have an important role in providing new drugs and prototypes. However, physicochemical and pharmacokinetics properties demand chemical optimization for many natural products to improve their safety and efficacy. Molecular modifications (MM) represent a successful approach to optimising such properties. Here, we describe the use of MM to enhance the properties of resveratrol. Thus, we described some strategies to find new resveratrol derivatives useful as sunscreen and treat sickle cell disease. Some examples are described, showing the role of MM in discovering new bioactive compounds.

1. MOLECULES FOR THE HUMAN HEALTH

Developing new drugs is a long-term and expensive process, which demands multiple approaches to minimize the risks involved. Among the various strategies used to discover new drugs, it is possible to highlight: a) serendipity; b) natural products; c) high-throughput screening (HTS); d) physiological approach - the study of biochemical pathways for selection of molecular targets; e) computational tools (direct and indirect methods); f) drug repositioning; g) molecular modifications, among others.

Usually, the different strategies are combined. For example, in the physiological approach, the study of biochemical pathways allows the identification of therapeutic targets. After obtaining the structures of these targets through X-ray crystallography or electron cryo-microscopy techniques, it is possible to use computational tools to plan ligands based on the knowledge of the receptor. As another example, a molecule derived from a natural substance with known pharmacological activity may require structural modifications to optimise its pharmaceutical, pharmacokinetic, or pharmacodynamic properties (Sliwoski et al., 2014).

Among the methods for discovering new drugs, molecular modification is very promising. This technique is employed in Pharmaceutical and Medicinal Chemistry and entails structural modifications of specific subunits present in the chemical structures of the compounds, which can alter physicochemical, conformational, and electronic properties, thereby promoting the optimization of the prototype compound.

The physician and physiologist James Black, winner of the Nobel Prize in Medicine and responsible for discovering drugs such as propranolol, famously said that one of the most fruitful ways to discover a new drug is from the structure of an old drug (Bradley, 2005). In this regard, molecular modification methods are appealing for optimising bioactive substances' medicinal, pharmacokinetic, or pharmacodynamic aspects. This strategy has been widely used to identify several drugs on the market.

In an interesting analysis of drug candidates in clinical trials between 2016-2017, it was observed that 43% of them come from molecular modification processes (Brown & Boström, 2018). In academia, it is a useful tool because it requires lower investments for research and has higher success rates than radical innovation.

The pharmaceutical industry, motivated by economic or competitive factors, uses molecular modification to develop analogues or "me-too" drugs. Thus, if a particular company has the knowledge to explore a certain therapeutic area, other companies can compete for that market through improvements

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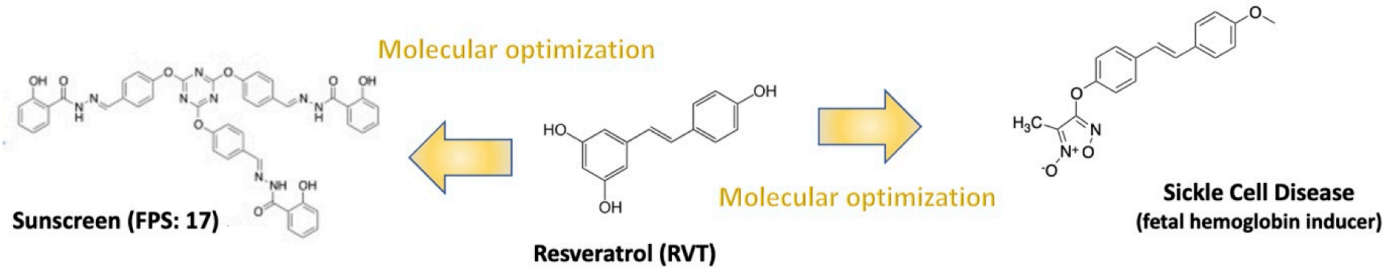

Figure 1. Molecular optimization of RVT to obtain new sunscreens and fetal hemoglobin inducer agents

in the properties of the existing drug, assuring therapeutic advantages to the newly developed products.

The analogs obtained in the molecular modification process commonly present a degree of structural similarity with the parental compound. Despite the similarity between similar biological properties, it is possible to present completely different biological activities.

Therefore, to support the structural similarity, several computational methods were developed to assist in identifying similar patterns to achieve the rational selection of compounds during the screenings. These programs recognize similarities in electronic, conformational and stereochemical patterns between compounds, signaling the degree of similarity between them, and can be a starting point in the molecular modification process (Kumar & Zhang, 2018; Sliwoski et al., 2014).

Several advantages are attributed to molecular modifications, including a) the discovery of analogues with biological activity equal to or superior to the parent drug; b) the possibility of knowing the pharmacological target and, from there, planning modifications based on the receptor structure; c) inferior complexity in the biological assays, since the tests had already been developed for the parental drug; d) lower R&D costs associated with low risk of failure; e) facilitated synthetic access due to the previous development of parental drug synthesis, among others.

Natural products are important in providing new drugs and prototypes for molecular modifications. One example is the natural product resveratrol (RVT), chemically trans-3,5,4'-trihydroxystilbene. This phytoalexin is synthesized by various plants, especially vines, in response to fungal infections or ultraviolet radiation. This substance, which is well known for its cardioprotective effects, has drawn attention from all over the world because of its function in controlling multiple transduction pathways that are present in a variety of diseases, including cancer, cardiovascular, neurodegenerative, and inflammatory diseases (Dutra et al., 2017). In the last ten years, the number of works on RVT) has increased, however, many of the reported pharmacological effects are due to nonspecific activities related to its disruptive effect on cellular membranes (Ingólfsson, 2014).

Some pharmacological properties described for RVT such as: antioxidant, anti-inflammatory and analgesic effects show benefits in Sickle Cell Disease (SCD). Among all the effects described, however, the most relevant for SCD seems to be the ability of the compound to increase the levels of fetal hemoglobin. In K562 erythroleukemic cell culture, RVT was able to induce γ-globin gene expression 4 times more than the drug hydroxyurea (Bianchi, 2009). Furthermore, RVT reduced TNF-α levels, the expression of adhesion molecules (VCAM-1 and ICAM-1) and inhibited platelet aggregation, showing multiple desirable effects in the treatment of SCD (Deng, 2011). Recently, we have synthesized new RVT derivatives with ability to release nitric oxide (Figure 1). All synthesized RVT derivatives, at a concentration of 100 μmol/Kg orally, showed analgesic effect in the abdominal writhing test induced by 0.6% acetic acid. Some of the compounds was effective as dipyrone in this in vivo assay. The most active compound was able to reduce TNF-α levels in monocyte culture to levels higher than RVT. In addition, it was able to inhibit the adhesion of neutrophils to the endothelium, an effect possibly related to the decrease of TNF-α. All compounds were evaluated for γ-globin expression using CD34+ cells. In this assay, the RVT derivative showed activity at a concentration of 12.5 μM comparable to RVT at a concentration of 25 μM. Neither genotoxic nor mutagenic effects were observed for all RVT derivatives. Due to the non-specific effect of RVT resulting from its ability to disturb membranes, an assay was carried out to assess whether the observed effects could be due to some non-specific activity. For this, the gramicidin-based fluorescence assay was chosen. This assay is validated in the literature and shows good correlation with other experimental data (Ingólfsson, 2014). RVT (10 μM) induced membrane perturbation, while RVT derivatives were not able to act as a membrane disruptor in the assay. These data suggested that the mechanism of action in increasing γ-globin expression for RVT derivatives is related to the action on specific targets.

Thus, some potential targets related to the regulation of γ-globin gene transcription were evaluated, such as transcription factors (BCL11A, IKAROS, LRF, SOX-6, FOG-1) and epigenetic mechanisms related to histone acetylation (H3 and H4) and inhibition of the enzyme histone deacetylase (HDAC). None of the mechanisms investigated was altered by the compound , except the inhibition of HDAC enzymes. Hybrid (137) demonstrated the ability to inhibit class I histone deacetylase enzymes, especially HDAC-8, with IC50 values of 700 nM (Bosquesi, 2020).

In addition to drugs, molecular modifications can be applied to different areas of Pharmaceutical Sciences, such as Cosmetology. Chronic exposure to ultraviolet (UV) radiation has harmful effects on the skin, being the main responsible for the development of skin cancer and photoaging. UV radiation has direct effects on genetic material through the formation of DNA adducts or increased production of reactive oxygen species, promoting tumor formation through several mechanisms.

It is described that antioxidants prevent DNA damage induced by reactive oxygen species (Jansen, 2013). Among these, RVT has potent antioxidant activity (Cadenas & Barja, 1999). Despite the antioxidant effect, RVT has a low sun protection factor (SPF). Thus, using the strategy of bioisosterism, the stilbenic subunit of RVT was replaced by N-acylhydrazone. Our research group has synthesized several RVT analogues, in which it was identified one compound with FPS value of five (Reis, 2014) (Figure 1). For this RVT derivative an increased absorption properties were found in the electromagnetic spectrum, thus being able to protect simultaneously against UVA (320-400 nm) and UVB (290-320 nm) radiation. In addition, the compound showed antioxidant activity comparable to RVT (Reis, 2014).

To optimize the FPS value of this first RVT derivative, the molecular replication strategy was performed. Specifically, the 1,3,5-triazine nucleus was used in the work to prepare triplicated RVT derivatives. Several substituents and their respective regioisomers were synthesized and evaluated. Among these, the one that showed the highest SPF was 17 (Figure 1). This compound also showed increased absorption capacity in the electromagnetic spectrum of UV, being also able to protect against UVA and UVB radiation. Moreover, it showed high thermal stability, undergoing decomposition only at temperatures above 230°C. Despite the increase in FPS, the compounds showed a reduction in the antioxidant effect compared to the RVT prototype (Reis, 2019).

In conclusion, molecular modification can contribute to the development of new drugs, especially in academia, reducing the risk of failure and research costs. The use of prototypes from natural sources, as exemplified by RVT here, is a promising approach to discover new chemical entities.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

J.L.B.P. and J.L.S. developed the conception of the presented idea and developed the theoretical framework; J.L.B.P. and J.L. contributed to the final version of the manuscript. J.L.S. did the overall supervision and critic review for the manuscript. Authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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