Proliferative effect of medicinal plants and laser on liver regeneration. A considerable experimental model: from an experimental model to clinical applications

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INTRODUCTION

The use of medicinal plants to treat human diseases has been performed for millennia. Nowadays, it is known that 80% of the world population have already taken medicinal plants and 30% were prescribed by physicians. In addition to this, it was estimated by the World Health Organization that 80% of the population of developing countries believe in traditional medicine (which consists of medicinal plants use in 85% of the cases) for primary health assistance. In China, particularly, 30 to 50% of all medicines used are originated from plants.

In Brazil, there are around 55 thousand species of registered plants; 20% of them are supposed to have medicinal effects. Besides such diversity, there are only few studies describing the mechanisms correlated to their effect. Considering that the study of their effects may lead to the development of new and cheaper kind of treatment for so many different diseases, we decided to assess the outcomes of the aqueous extract of 2 plants from northeastern Brazil on liver regeneration following 67% partial hepatectomy.

*Sid a cordifolia* L. (Malvaceae) is popularly known as “malva-branca” (white mallow) or “malva-branca-sedosa” (silky white mallow) in Brazil. It grows as a bush of up to 2 m in height. The leaves are light green, cordiform, serrated and oval-elongated, and the pedunculated flowers are arranged in axillary or terminal racemes. In traditional medicine, the plant is used for the treatment of stomatitis, blenorrhea, asthmatic bronchitis and nasal congestion. In the state of Sergipe, it has been recommended for the treatment of inflammation, pain, cancer, bacterial infections and wound healing.

The effectiveness of the extract of *Sid a cordifolia* leaves as analgesic, anti-inflammatory (inhibition of prostaglandin synthesis) and hypoglycemic has been reported. *Hyptis pectinata* (L.) Poit (Lamiaceae), popularly known in Brazil as “sambacaitá” or “canudinho”, is an herbaceous plant with opposing crossed, whole and aromatic leaves. Its flowers are small, clustered into axillary inflorescences, hermaphrodite, pentamer, strongly zygomorphous and bilabiate. It is popularly used to treat rhinopharyngitis, nasal congestion, certain skin diseases, gastric disorders, fever and bacterial infections. In the state of Sergipe, it has been recommended for the treatment of inflammation, pain, cancer, bacterial infections and wound healing.

The essential oil of the plant contains 33 compounds. Monoterpenes are the most common (95.8%). The main constituents are p-cymene, thymol and ß-terpinene. Together, they correspond to 68% of the total. During chromatography, thymol was considered the main factor for the antiseptic property of this plant.

Besides the study of these 2 plants on liver regeneration, we decided to associate laser therapy with *Hyptis pectinata* leaves extract. Low intensity laser therapy has been widely used in all medical fields due to its therapeutic effects on reparative process. After penetration of the laser in the liver, stimulatory or inhibitory effects are common in biostimulation by light depending on the dose or wave length. It seems to be more likely that laser target organelle is also the mitochondria. Biological responses of cells to laser radiation are caused by physical and chemical changes in photoacceptor molecules, components of respiratory chains like cytochrome C oxidase and NADH-dehydrogenase.

The study of these substances and laser on liver regeneration is extremely important due to the essential function of this organ. So, an accelerated liver regeneration process is required when this organ is submitted to partial hepatectomy in order to resect tumors; to improve its growth after transplantation from little donors; or to restore the hepatic mass following extensive injury. A rat model was chosen due to its similarity to the human body.

THE FACT AND NOT AN EPIPHENOMENON

Well, according to Stephenson, all drugs exert a dose-dependent effect on their targets. However, this process depends on the amount of available receptors and the physical and chemical properties of the substances. This theory is applied to pharmacology. On the other hand, phytotherapy is not fully understood. It is possible that, at some concentrations, certain compounds of the plant extract could act in synergism and cause a significant effect. At lower or higher concentrations, these compounds could be antagonized by different ones.

Liver regeneration was stimulated by *Hyptis pectinata* at doses of 100 mg/kg. On the other hand, the enhancement effect was not observed by higher concentrations (200 and 400 mg/kg). This might be explained by hepatocellular membrane receptors saturation or a possible blockage of some stage of the metabolic reaction. It may lead to an uncoupled mitochondrial function which is able to cause relative decrease in liver regeneration and function, as verified in the copaiba oleoresin study.
The association between *Hyptis pectinata* extract at 200 mg/kg and laser therapy brought about a significant increase in liver regeneration in comparison to each of them alone or their absence (control).

There are two main alternatives to be considered as a possible explanation for the observed effects. First, the used substance (*Hyptis pectinata*) may have a strong absorption of light. Therefore, it may be excited during irradiation, leading to the formation of more reactive radicals or molecules. These final products could be responsible for accelerating the metabolic level and resulting in regeneration effects of hepatic *Hyptis pectinata*. In this case, the presence of *Hyptis pectinata* as one of the target for laser effects, working as an added chromophor.

The second possibility relies on the already recognized. The electron transport from the mitochondrial membrane. The electrochemical H gradient across the inner mitochondrial membrane injury. And besides, *Hyptis pectinata* in vitro, does not cause mitochondrial inner membrane injury.

We expect to have established a new perspective on the study of liver regeneration, medicinal plants and laser therapy. If this model could be put into practice in human beings, a new approach to treat liver diseases and to improve hepatic proliferation after injury would be developed. However, further studies are needed in order to determine the exact mechanisms related to our findings. Additionally, it is important to isolate the active compounds responsible for these results.

Concerning the study of *Hyptis pectinata* leaves aqueous extract on liver mitochondrial respiratory, it was found that it caused a statistically significant decrease in state 3 at 0.05, 0.1 and 0.2 mg/mg prot and RCR (respiratory control ratio) at 0.05, 0.1 and 0.2 mg/mg prot. Respiratory state 4 was not altered by the increasing concentrations.

Although the mechanism of biostimulation or inhibition remains to be elucidated, some recent studies indicate that mitochondria may be the target organelle of plants. The critical role played by mitochondria in the maintenance of cellular energy metabolism has long been recognized. The electron transport from the oxidation of NADH and reduced FADH₂ to O₂ is tightly coupled to the synthesis of ATP. This transport occurs through protein-bound redox centers, from complex I (NADH-coenzyme Q reductase) or II (succinate-coenzyme Q reductase) to III (coenzyme cytochrome e reductase) and then to IV (cytochrome e oxidase). The free energy released by this transport is conserved by pumping out protons in order to create an electrochemical H gradient across the inner mitochondrial membrane. The electrochemical potential of this gradient is then harnessed in the synthesis of ATP by complex V (ATP synthase): this process is known as oxidative phosphorylation.

In conclusion, we found that *Sida cordifolia*, *Hyptis pectinata* and laser therapy in association cause an outstanding stimulation of liver regeneration. And besides, *Hyptis pectinata*, when studied in vitro, does not cause mitochondrial inner membrane injury.

**References**


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