

# Effects of low-power light therapy on wound healing: LASER x LED\*

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**Abstract:** Several studies demonstrate the benefits of low-power light therapy on wound healing. However, the use of LED as a therapeutic resource remains controversial. There are questions regarding the equality or not of biological effects promoted by LED and LASER. One objective of this review was to determine the biological effects that support the use of LED on wound healing. Another objective was to identify LED's parameters for the treatment of wounds. The biological effects and parameters of LED will be compared to those of LASER. Literature was obtained from online databases such as Medline, PubMed, Science Direct and Scielo. The search was restricted to studies published in English and Portuguese from 1992 to 2012. Sixty-eight studies in vitro and in animals were analyzed. LED and LASER promote similar biological effects, such as decrease of inflammatory cells, increased fibroblast proliferation, stimulation of angiogenesis, granulation tissue formation and increased synthesis of collagen. The irradiation parameters are also similar between LED and LASER. The biological effects are dependent on irradiation parameters, mainly wavelength and dose. This review elucidates the importance of defining parameters for the use of light devices.

**Keywords:** Light; Phototherapy; Wound healing

## INTRODUCTION

A wound is characterized by the interruption on the continuity of a body tissue. It can be caused by any type of physical, chemical and mechanical trauma or triggered by a medical condition.<sup>1</sup> Cutaneous wounds are relatively common in adults and their incidence seems to increase in parallel with the advances in life expectancy in the population.<sup>2</sup>

The therapeutic approach to wound healing consists of preventive measures such as health professional continuing education, family counseling and guidelines to a proper patient nutrition. The use of medicinal plants, administration of essential fatty acids, calcium alginate, antiseptics and degerming products, activated carbon, semi-permeable films, biological collagen, cell growth factors, hydropolymer, hydrogel and hydrocolloid substances, proteolytic enzymes, sulfadiazine silver, gauze dressings, bandages for skin protection and compression are also advocated.<sup>3</sup> Physical treatments such as therapeutic

ultrasound and electrotherapy are cited likewise in the literature as important adjuncts in wound management.<sup>4,5</sup> These therapies seem to be advantageous but they have limitations and do not always achieve satisfactory results.

Wounds that are difficult to heal represent a serious public health problem. The lesions severely affect the quality of life of individuals due to decreased mobility and substantial loss of productivity; they can also cause emotional damage and contribute to increase the burden of public expenditures in healthcare.<sup>6</sup>

The need to care for a population with poorly healing wounds is a growing challenge that requires innovative strategies. An approach that stands out in the treatment of these lesions is low-power light therapy, promoted by light devices such as LASER (Light Amplification by Stimulated Emission of Radiation) and LED (Light Emitting Diode).

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The therapeutic benefits of LASER light in the treatment of wounds have been reported since the 1960s and those of LED light only since the 1990s.<sup>7,8</sup> However, many of the results described show inconsistency, mainly due to methodology bias or lack of standardization in the studies. Furthermore, the use of LED as a therapeutic resource remains controversial. There are questions regarding the equality or not of biological and therapeutic effects promoted by LED and LASER resources, but also regarding the appropriate parameters to each of these light sources.

This study aimed to determine, through a literature review: 1 - the biological effects that support the use of light sources such as LED in the treatment of wounds and 2 - the light parameters (wavelength and dose) suitable for the treatment of wounds with LED light sources. The biological effects and light parameters of LED will be compared to those of LASER in order to verify the similarity (or not) regarding wound treatment.

## MATERIALS AND METHODS

A literature search was performed in Medline, PubMed, SciELO and Science Direct databases. The literature search was restricted to studies published in English and Portuguese in the period of 1992-2012. The keywords used were "low level laser therapy", "laser", "light emitting diode", "LED", "phototherapy", "wound healing", "fibroblast", "collagen" and "angiogenesis" combined with each other.

## RESULTS

Sixty-eight studies were analyzed, including 48 on LASER light, 14 related to LED light and 6 for both types of light (Tables 1 to 3). According to data presented on table 1, 16 of the 48 studies on the effects of LASER light were *in vitro* and 32 were performed in animals.<sup>9-56</sup> The use of different wavelengths (532-1064 nm) was verified, with the most utilized spectral range being between 632.8 and 830 nm. Doses ranging from 0.09 to 90 J/cm<sup>2</sup> were used, predominating the values from 1 to 5 J/cm<sup>2</sup>. One study did not cite the dose value used.<sup>48</sup> The biological effects promoted were reduction of inflammatory cells, increased proliferation of fibroblasts, stimulation of collagen synthesis, angiogenesis inducement and granulation tissue formation. It was noted in a study that the dose of 4 J/cm<sup>2</sup> was more effective than 8 J/cm<sup>2</sup>.<sup>14</sup> Furthermore, doses of 10 and 16 J/cm<sup>2</sup> promoted inhibitory effects.<sup>20,25,29,34</sup>

Eight of the 14 studies on the effects of LED light were *in vitro* studies and 6 performed in animals, as shown in table 2.<sup>37-70</sup> Wavelengths ranging 456-880 nm were used, with spectral range from 627 to 670 nm predominating. Doses ranged from 0.1 to 10 J/cm<sup>2</sup>,

and 4 J/cm<sup>2</sup> was the predominant dose. However, not all studies reported the dose applied.<sup>64,66,67,68</sup> Biological effects observed were reduction of inflammatory cells, increased fibroblast proliferation, collagen synthesis, stimulation of angiogenesis and granulation tissue formation, these being similar to the ones observed in studies with LASER.

Table 3 shows six studies comparing the biological effects of LASER and LED lights.<sup>71-76</sup> Two of the studies were *in vitro* and 4 were performed in rats. It has been noticed that wavelengths varied from 460 to 950 nm, with the range of 630-790 nm being the most utilized both in LASER and LED studies. Doses ranging from 0.1 to 10 J/cm<sup>2</sup> were used, with predominance of doses up to 5 J/cm<sup>2</sup>. All studies reported similar effects between LASER and LED, such as increased fibroblast proliferation and stimulation of angiogenesis.

## DISCUSSION

Since the introduction of photobiomodulation in healthcare, the effectiveness and applicability of light resources for the treatment of skin wounds have been extensively investigated both *in vitro* and *in vivo*. Nevertheless, the biological mechanisms that support the actions of low intensity light in tissues are still not clearly elucidated. While some studies report an increase in cellular proliferation of several cell types including fibroblasts, endothelial cells and keratinocytes, conflicting results about the clinical benefits of using light on skin wounds are found in the literature.

The way light interacts with the biological tissues will depend on the characteristics and parameters of light devices, mainly the wavelength and dose, and also the optical properties of the tissue.

Regarding the characteristics of light devices, LASER consists of a resonant optical cavity and different types of active media such as solid, liquid or gaseous materials, in which processes of light generation occur through the passage of an electric current.<sup>77</sup> Potency in the range of 10<sup>-3</sup> to 10<sup>-1</sup> W, wavelength from 300 to 10,600 nm, pulse frequency from 0 (continuous emission) to 5,000 Hz, pulse duration and pulse interval from 1 to 500 milliseconds, total radiation from 10-3000 seconds, intensity between 10<sup>-2</sup> and 10<sup>0</sup> Wcm<sup>-1</sup> and dose from 10<sup>-2</sup> to 10<sup>2</sup> Jcm<sup>-2</sup> characterized LASER as a low potency device.<sup>78</sup>

On the other hand, LED is a diode formed by p-n junctions (p-positive, n-negative) that, when directly polarized, causes electrons to cross the potential barrier and recombine with holes within the device. After the spontaneous recombination of electron-hole pairs, the simultaneous emission of photons occurs. The physical mechanism by which LED emits light is spontaneous light emission. The light-emitting

TABLE 1: Biological effects of LASER light on cutaneous wounds

Study	Model	Wavelength (nm)	Dose (J/cm <sup>2</sup> )	Biological effects
Lubart <i>et al.</i> <sup>9</sup>	In vitro	632	9; 15; 30; 60; 90	+
		780	7; 18; 36; 72	
Yu <i>et al.</i> <sup>10</sup>	Mouse	630	5	+
Almeida-Lopes <i>et al.</i> <sup>11</sup>	In vitro	670; 692; 780; 786	2	+
Reddy <i>et al.</i> <sup>12</sup>	Rat	632,8	1	+
Pereira <i>et al.</i> <sup>13</sup>	In vitro	904	3; 4; 5	+
Medrado <i>et al.</i> <sup>14</sup>	Rat	670	4; 8	+
Pugliese <i>et al.</i> <sup>15</sup>	Rat	670	4; 8	+
Reddy <sup>16</sup>	Rat	904	1	+
Byrnes <i>et al.</i> <sup>17</sup>	Rat	632.8	4; 5; 7.2	+
Nascimento <i>et al.</i> <sup>18</sup>	Rat	670; 685	10	+
Ribeiro <i>et al.</i> <sup>19</sup>	Rat	632.8	1	+
Hawkins and Abrahamse <sup>20</sup>	In vitro	632.8	0.5; 2.5; 5; 10	+
Maiya <i>et al.</i> <sup>21</sup>	Rat	632.8	4.8	+
Moore <i>et al.</i> <sup>22</sup>	In vitro	625 - 675; 810	10	+
Poon <i>et al.</i> <sup>23</sup>	In vitro	532	0.8	+
Carvalho <i>et al.</i> <sup>24</sup>	Rat	632.8	4	+
Hawkins and Abrahamse <sup>25</sup>	In vitro	632.8	2.5; 5; 16	+
Rabelo <i>et al.</i> <sup>26</sup>	Rat	632.8	10	+
Araújo <i>et al.</i> <sup>27</sup>	Mouse	632.8	1	+
Hawkins and Abrahamse <sup>28</sup>	In vitro	632.8; 830	5	+
Hourel and Abrahamse <sup>29</sup>	In vitro	632.8	5; 16	+
Mirzaei <i>et al.</i> <sup>30</sup>	In vitro	632.8	0.09; 1; 4	+
Rezende <i>et al.</i> <sup>31</sup>	Rat	830	1,3; 3	+
Viegas <i>et al.</i> <sup>32</sup>	Rat	685; 830	4	+
Yasukawa <i>et al.</i> <sup>33</sup>	Rat	632.8	2.09; 4.21	+
Hourel and Abrahamse <sup>34</sup>	In vitro	632.8; 830	5; 16	+
Medrado <i>et al.</i> <sup>35</sup>	Rat	670	4	+
Meireles <i>et al.</i> <sup>36</sup>	Rat	660; 780	20	+
Reis <i>et al.</i> <sup>37</sup>	Rat	670	4	+
Gungormus and Akyol <sup>38</sup>	Rat	808	10	+
Skopin and Molitor <sup>39</sup>	In vitro	980	3.1 - 14.4	+
Carvalho <i>et al.</i> <sup>40</sup>	Rat	660	4	+
Chung <i>et al.</i> <sup>41</sup>	Mouse	660	1.9 - 2.5 3.7 - 5.0 7.4 - 10	+
Gonçalves <i>et al.</i> <sup>42</sup>	Rat	830	30; 60	+
Gonçalves <i>et al.</i> <sup>43</sup>	Rat	830	30; 60	+
		904	4	
Guirro <i>et al.</i> <sup>44</sup>	Rat	670	4; 7	+
Hourel and Abrahamse <sup>45</sup>	In vitro	632.8; 830	5	+
Laćakova <i>et al.</i> <sup>46</sup>	Rat	670	5	+
Medeiros <i>et al.</i> <sup>47</sup>	Rat	655	12	+
Hussein <i>et al.</i> <sup>48</sup>	Rabbit	890	-----	+
Silveira <i>et al.</i> <sup>49</sup>	Rat	660; 904	1; 3	+
Weng <i>et al.</i> <sup>50</sup>	In vitro	532	35	+
		1064	1.2	
Basso <i>et al.</i> <sup>51</sup>	In vitro	780	0.5; 1.5; 3; 5; 7	+
Crisan <i>et al.</i> <sup>52</sup>	In vitro	830; 980	5.5	+
Dawood and Salman <sup>53</sup>	Mouse	650	38.2; 57.3	+
Fahimipour <i>et al.</i> <sup>54</sup>	Mouse	632.8; 830	4; 7.5	+
Gonçalves <i>et al.</i> <sup>55</sup>	Rat	830	30; 90	+
Nunez <i>et al.</i> <sup>56</sup>	Rat	660	1; 4	+

TABLE 2: Biological effects of LED light on cutaneous wounds

Study	Model	Wavelength (nm)	Dose (J/cm2)	Biological effects
Whelan <i>et al.</i> <sup>57</sup>	In vitro	670; 728; 880	4; 8	+
Vinck <i>et al.</i> <sup>58</sup>	In vitro	570	0.1	+
Weiss <i>et al.</i> <sup>59</sup>	In vitro	590	0.1	+
Huang <i>et al.</i> <sup>60</sup>	In vitro	630	1; 2	+
Lanzafame <i>et al.</i> <sup>61</sup>	Mouse	670	5	+
Agnol <i>et al.</i> <sup>62</sup>	Rat	640	6	+
Tada <i>et al.</i> <sup>63</sup>	In vitro	627	1; 2; 4; 8; 10	+
Komine <i>et al.</i> <sup>64</sup>	In vitro	627	4	+
Meyer <i>et al.</i> <sup>65</sup>	Rat	515-525 620-630	-----	+
Sousa <i>et al.</i> <sup>66</sup>	Rat	460; 530; 700	10	+
Adamskaya <i>et al.</i> <sup>67</sup>	Rat	470; 629	-----	+
Lim <i>et al.</i> <sup>68</sup>	In vitro	635	-----	+
Cheon <i>et al.</i> <sup>69</sup>	Rat	470; 525; 633	-----	+
Fushimi <i>et al.</i> <sup>70</sup>	In vitro	456; 518; 638	0.2; 0.3; 0.6	+

TABLE 3: Biological effects of LED and LASER light on cutaneous wounds

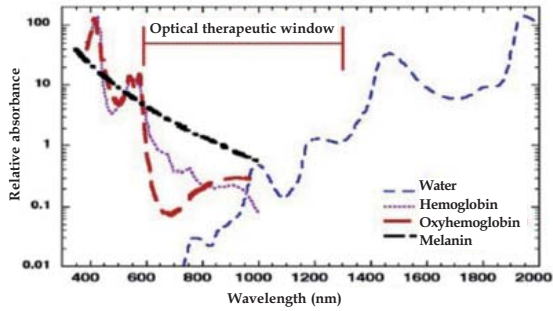
Study	Model	Type of light	Wavelength (nm)	Dose (J/cm2)	Biological effects
Vinck <i>et al.</i> <sup>70</sup>	In vitro	LASER	830	1	+
		LED	570	0.1	
			660	0.53	
			950	0.53	
Corazza <i>et al.</i> <sup>71</sup>	Rat	LASER	660	5	+
		LED	635	20	
Volpato <i>et al.</i> <sup>72</sup>	In vitro	LASER	660	4; 8	+
			780	5; 10	
		LED	637	4; 8	
Nishioka <i>et al.</i> <sup>73</sup>	Rat	LASER	660	5	+
		LED	630		
Sampaio <i>et al.</i> <sup>74</sup>	Rat	LASER	660	10	+
		LED	700		
Sousa <i>et al.</i> <sup>75</sup>	Rat	LASER	660; 790	10	+
		LED	460; 530; 700		

diodes convert the electrical current in a light spectrum, a process called electroluminescence.<sup>79</sup> LEDs usually operate with outputs in the range of milliwatts and therefore are usually set up on small chips or connected to small light bulbs.<sup>80</sup>

The variable characteristics and parameters of light devices is one of the factors that complicate the interpretation of research results about the effects of low intensity light on skin wounds. As observed in this study, there is discordance between the types of light and parameters used in studies. This fact may limit the decision-making process regarding the role of light in treating wounds since photobiomodulator effects are parameter-dependent.

Energy absorption is the primary mechanism that allows light from LASER or LED to produce biological effects in the tissue. Light absorption is dependent on wavelength and the main tissue chromophores (hemoglobin and melanin) strongly absorb wavelengths shorter than 600 nm. For these reasons, there is a therapeutic window in the optical spectral range of red and near infrared, wherein the efficiency of light penetration in the tissue is maximum (Figure 1).<sup>81</sup>

Fifty-nine of the 68 studies reviewed applied LASER or LED inside the optical therapeutic window and 9 applied them in the range of blue or green, and even so biological effects were observed. Although light in the blue and green wavelengths range can



Source: Schindl A, et al. 2000.

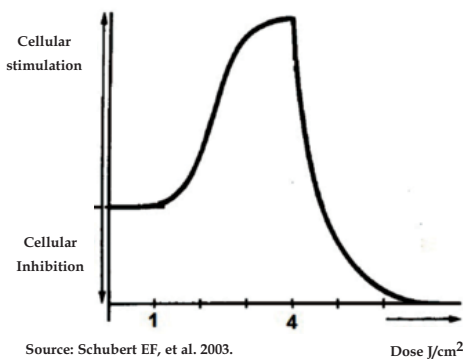
FIGURE 1: Optical therapeutic window

achieve significant effects in cells, the use of low power light in animals and humans involves almost exclusively light in red and near infrared wavelengths.<sup>81</sup> Historical issues, mainly cost and availability may be related to this fact.

As noted in Tables 1, 2 and 3 studies applied LASER or LED with doses around 0.09 to 90 J/cm<sup>2</sup>. The most significant biological effects were seen with predominant dose values, i.e. up to 5 J/cm<sup>2</sup>, which are within the Arndt-Schultz curve (Figure 2). According to Sommer et al, very low doses do not promote biological effects, while higher doses result in inhibition of cellular functions.<sup>82</sup> The energetic state of the cell, i.e. the physiological condition of the tissue in treatment is therefore critical to determine which dose to use.

The mechanism of light action on the cellular level that supports its biological effects is based on photobiological reactions. A photobiological reaction involves the absorption of a specific wavelength of light by photoreceptor molecules.<sup>83</sup>

There is evidence that wavelengths in the spectral range from red to near infrared are absorbed by cytochrome c oxidase.<sup>83,84</sup> In the study by Karu and Kolyakov action spectra of monochromatic light from



Source: Schubert EF, et al. 2003.

FIGURE 2: Arndt-Schultz Curve

580 to 860 nm were analyzed.<sup>85</sup> The authors noted four active spectral regions, two in the red range (peaks from 613.5 to 623.5 nm and 667.5 to 683.7 nm) and two infrared (peaks from 750.7 to 772, 3 nm and 812.5 to 846.0 nm). In addition, they also observed the absorption by cytochrome c oxidase in these four bands. The authors concluded that cytochrome c oxidase could absorb light in different spectral bands (red and near infrared), probably in the binuclear centers CuA and CuB (oxidized forms).

Photobiological reactions can be classified into primary and secondary. Primary reactions derive from the interaction between photons and the photoreceptor, and they are observed in a few seconds or minutes after the irradiation of light. On the other hand, secondary reactions are effects that occur in response to primary reactions, in hours or even days after the irradiation procedure.<sup>84,86</sup>

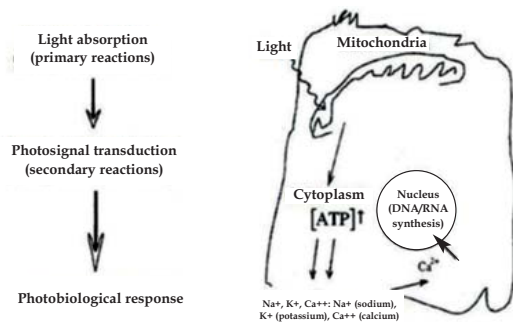
The primary reactions of light action on photoreceptors are not yet clearly established, but there are some hypotheses. After the absorption of light in the irradiated wavelength, cytochrome c oxidase displays an electronically excited status, from which it alters its redox status and causes the acceleration of electron transfer in the respiratory chain.<sup>87</sup> Another hypothesis is that a part of the electronically excited status energy is converted into heat, causing a localized and transient heating in photoreceptors.<sup>88</sup> A third assumption would be that when enabling the flow of electrons in the respiratory chain by light irradiation, an increase in the production of superoxide anion can be expected.<sup>89</sup> A fourth reaction formula assumes that porphyrins and flavoproteins absorb photons and generate reactive species of singlet oxygen.<sup>90</sup> It has also been proposed that light can reverse cytochrome c oxidase inhibition through nitric oxide and thereby increase the rate of respiration.<sup>91</sup>

The mechanism of secondary photobiological reactions is determined by transduction (energy transfer from one system to another) and photosignal amplification leading to photoresponse. This means that effects derived from primary reactions are amplified and transmitted to other parts of the cell, resulting in physiological effects such as alterations in cell membrane permeability with changes in intracellular calcium levels, increased cellular metabolism, DNA and RNA syntheses, fibroblast proliferation, activation of T lymphocytes, macrophages and mast cells, increased synthesis of endorphins and decreased bradykinin.<sup>85</sup>

Secondary reactions are responsible for the connection between response to light action by photoreceptors located inside the mitochondria and the effects located in the nucleus or different phenomena in other cell components. This process makes it possi-

ble to apply a very small amount of light to produce clinically significant effects on tissues.<sup>92</sup>

In short, light absorption depending on the wavelength, causes primary reactions on the mitochondria. These are followed by a cascade of secondary reactions (photosignal transduction and amplification) that occur in the cytoplasm, membrane and nucleus as shown by the Karu model (Figure 3).



Source: Huang YY, et al. 2009.

FIGURE 3: Karu Model

Nevertheless, there is a hypothesis about a modification in the Karu model. It is believed that the red light is absorbed by cytochrome-c oxidase inside the mitochondria, while the infrared wavelength is absorbed by specific cell membrane proteins directly affecting membrane permeability; both pathways lead to the same photobiological end response.<sup>93</sup>

Sources like LASER differ from LED ones because of a characteristic known as coherence. This feature is related to stimulated emission mechanisms, with LASER light being formed by same frequency,

direction and phase waves.<sup>94</sup> Some authors believe that coherence plays a role in the production of light therapy derived benefits, and LED (not coherent) would be less efficient than LASER (coherent) or even unable to promote therapeutic effects.<sup>95</sup>

The reviewed studies, however, have shown that LED light can be as effective as LASER, since both have similar biological effects, with no significant difference between them. The cellular response to photostimulation is not associated with specific properties of LASER light, such as coherence.<sup>96</sup> According to Karu, the property of coherence is lost during the interaction of light with biological tissue, not being thus a prerequisite for the process of photostimulation or photoinhibition.<sup>86</sup>

More clinical studies, especially with LEDs, must be performed in order to assess the adequacy of parameters commonly used experimental *in vitro* and animal studies to the clinical practice, since, in the relevant literature, there is a diversity in methodology, as well as differences in wavelength, dose and types of study.

## CONCLUSION

The reviewed studies show that phototherapy, either by LASER or LED, is an effective therapeutic modality to promote healing of skin wounds. The biological effects promoted by these therapeutic resources are similar and are related to the decrease in inflammatory cells, increased fibroblast proliferation, angiogenesis stimulation, formation of granulation tissue and increased collagen synthesis. In addition to these effects, the irradiation parameters are also similar between LED and LASER. Importantly, the biological effects are dependent on such parameters, especially wavelength and dose, highlighting the importance of determining an appropriate treatment protocol. □

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