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The Role of Leptin Hormone, Neuropeptide Y, Ghrelin and Leptin/Ghrelin ratio in Obesogenesis

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Abstract

In addition to energy storage, the adipose tissue plays multiple important roles, particularly the secretion of biomolecules such as leptin that participate in the neuroendocrine regulation of appetite. Therefore, this review sought to understand the influence of leptin on the genesis of obesity. A systemic review of the literature was conducted using articles published in English between 2016 and 2022. Ten experimental studies that introduced new approaches for treating leptin-resistant individuals were selected. The results showed that a structured food plan with a negative energy balance combined with a regular physical activity routine remains the best way to combat obesity and leptin resistance problems. It is possible to conclude that leptin resistance contributes to maintaining obesity. However, to date, there remains a lack of evidence that demonstrates a direct relationship between the poor function of this peptide and the genesis of obesity.

Keywords: Appetite, leptin, obesity, adipose tissue.

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Introduction

The World Health Organization (WHO) defines obesity as a worldwide epidemic and describes it as a multifactorial chronic inflammatory disease caused by the accumulation of adipose tissue in the body [1]. This high-fat concentration affects the health of individuals of any age through histopathological complications [2].

The aetiology of obesity is not easy to identify due to its characterisation as a multifactorial disease that results from complex interactions between behavioural, cultural, genetic, physiological, and psychological factors [3].

Population studies have demonstrated that excess adipose tissue, particularly in the abdominal region, is closely related to the risk of chronic non-communicable diseases that promote increased morbidity and mortality. This association arises with an increase in the body mass index (BMI) [3]. Most of these diseases are related to the function of adipose tissue as an endocrine organ, as adipocytes synthesize various biomolecules, including adiponectin, glucocorticoids, tumor necrotic factor (TNFa), sex hormones, interleukin-6 (IL-6), and leptin, which function in the metabolism and control of various systems [4].

Clinical trials have shown failures in leptin administration as an effective therapeutic approach in treating obesity, although it attenuates the neuroendocrine and metabolic changes induced by weight loss. Many studies have reported that the primary role of leptin is to signal Hunger (through a decrease in leptin levels) and, consequently, produce behavioural and metabolic responses [4].

Scientific literature has also shown that adipose cells can produce several substances and do not just store triglycerides. Among the substances synthesized by lipocytes, leptin is an important regulator of satiety [5].

Understanding appetite regulation mechanisms allows the development of novel treatments for obesity, thereby elucidating the relationship between hormonal plasma levels and obesity, thus, linking the organism's physiology with human eating behaviour and the influence of one on the other [6].

Animal studies have shown that by restricting food intake in obese animals, neurotransmitters in the hypothalamus undergo acute changes that result in hyperphagia, increased appetite, and, consequently, weight loss [7].

Leptin production increases proportionally with adipose tissue levels. However, its satietogenic effects are inefficient in the treatment of obesity. Such observations may indicate a possible factor

That limits diet adhesion and facilitates weight gain [8]. These findings demonstrate the need for an in-depth understanding of the mechanisms by which leptin influences weight gain and favours the development of obesity. Thus, the main objective of this study was to demonstrate the influence of leptin in the process of obesity and identify its roles in physiological and behavioural reactions and the genesis of obesity [9].

METHODOLOGY

Study design

A Systematic review of the literature on the influence of leptin on the process of obesity was performed

This research conclusion consisted of a Systemic review from January to May 2022. The review included scientific articles from 2016 to 2022, including the first definitions of the subject in the literature to the most recent scientific research. This study uses different sources of analysis and information to support the objectives and generate conclusions from the author's perspective.

This research was based on PubMed/Medline, DOAJ, and Google Scholar data. Search keywords were leptin and obesogenic; the correlated variables were obesity, adults, and leptin; we excluded the leptin gene, leptin phenotypes in pregnant women, and untrusted articles.

Data Analysis

The inclusion criteria were articles published in the last six years in Arabic or English, available in the public domain on the subject, original research published in scientific journals in full format, monographs, articles, dissertations, and theses. The exclusion criteria were documents inconsistent with the subject, documents of reflection, opinions, and reviews. After applying these criteria, articles related to the theme and the data organization were selected for a full reading.

LITERATURE REVIEW

Initially, 13020 articles were identified using keywords, and this was reduced to 9303 after selecting the studies on humans alone. Articles published between 2016 and 2021 were retained, leaving 1245 publications. Among these, 203 were randomised clinical trials and based on the inclusion and exclusion criteria, 10 articles were selected for the present review, as described in Figure 1

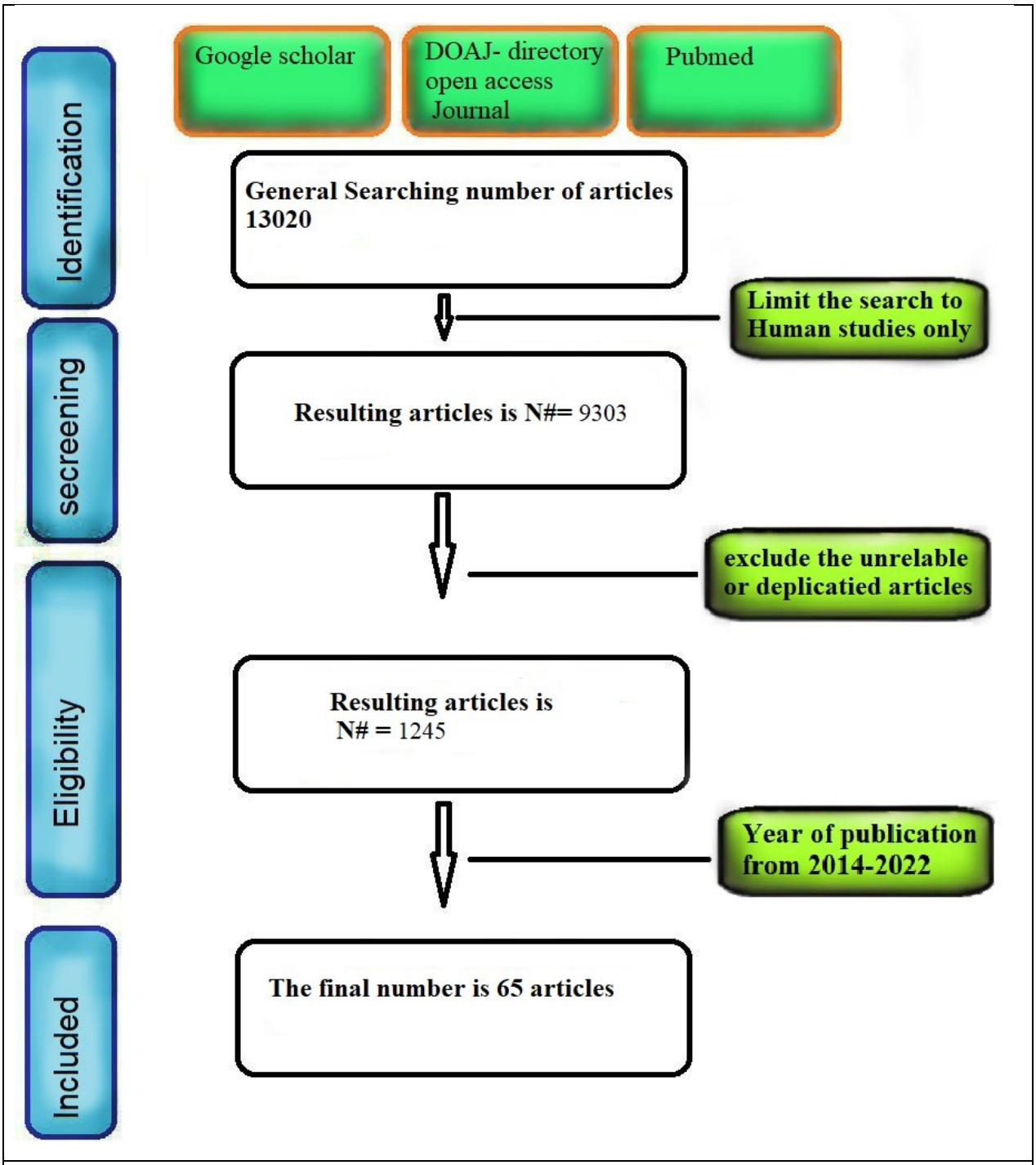

Figure 1. Description of the selection of articles.

LEPTIN AND OBESITYGENESIS

Obesity is a multifactorial pandemic that has spread worldwide due to the consumption of ultra-processed foods. Among some people, eating habits act of eating is becoming mechanical and automatic. However, there are diverse factors that cause obesity, and these include genet-

ic, psychological, metabolic, and environmental factors [1,9]. With the increase in the obese population, there is an imminent need to study and better understand the regulatory mechanisms of Hunger and satiety. Appetite, the motivator of eating, involves a series of complex neurocircuits that influence an individual's perception of their nutritional status and signals for Hunger. The process of Hunger begins with a hunger-stimuli, during which the release of several signals guarantees the completion of the act of eating. The primary signs of Hunger arise in the stomach via electrical impulses along the vagus nerve with the action of the hormone ghrelin and a hypoglycaemic state [10]. When the feeding process stops, and the individual is overcome by the feeling of being full, a physiological state of satiety occurs.

Satiety dictates the amount of food ingested during the meal. Nutrient chemoreceptors and those responsible for stretching the stomach walls react to food intake, informing the brain through signaling [11].

Hormones such as insulin, glucagon, leptin, and ghrelin regulate appetite and satiety. However, several other peptides and hormones, including glucagon-like peptide-1 (GLP-1), gastric inhibitor peptide (GIP), and Y.Y. peptide (PYY), are found in the gastrointestinal environment and act on satiety [12]. Several tissues secrete ghrelin, but its expression mainly occurs in the oxyntic glands of the stomach. Food deprivation initiates the secretion of gastric ghrelin. When released, this hormone acts on neuronal receptors, recruiting the enzyme protein kinase activated by adenosine monophosphate (AMP-K), releasing calcium (Ca^{2+}) from internal reserves. This response, which may last for hours after the initial presence of ghrelin, causes the excitation of neurons sensitive to ghrelin to up to the orexigenic neurons of agouti-related protein (AGRP). Monteiro et al. (2019) explained that leptin is an adipogenic signal sent to the brain with the function of regulating the energy balance; it acts on the hypothalamus [13], primarily in the arched nucleus, which has two populations of neurons, namely the orexigen [14], which is responsible for secreting the neuropeptide Y and AgRP(agouti-related protein) and anorexigens, which secretes cart (transcript regulated by cocaine and amphetamine) and α-MSH (Melanocyte peptide), derived from POMC (proopiomelanocortin). Therefore, an increased plasma concentration of leptin results in the inhibition of NPY/AgRP neurones and stimulation of α-MSH/CART neurones, leading to decreased food intake [15].

In contrast, when there is a decrease in leptin concentration, anorexigenic neurones are not sufficiently stimulated, and orexigenous neurones are no longer inhibited, leading to an increase in food intake, as illustrated in Figure 2. In individuals with obesity, this mechanism is impaired, resulting in the possibility of high levels of circulating leptin and the absence of sensi-

tivity through exogenous administration [16]. This inefficiency of leptin in promoting its anorexigenic effect in obese individuals is called leptin resistance [17]. One possible explanation for this resistance to leptin in obese individuals is increased leptin-LEPR signaling, with changes in neural circuitry in the hypothalamus. In this context, an increase in leptin-LEPR signaling in the hypothalamic region could cause an increase in local cytokine production, consequently potentiating inflammatory signaling in cells in this area [4,5,17].

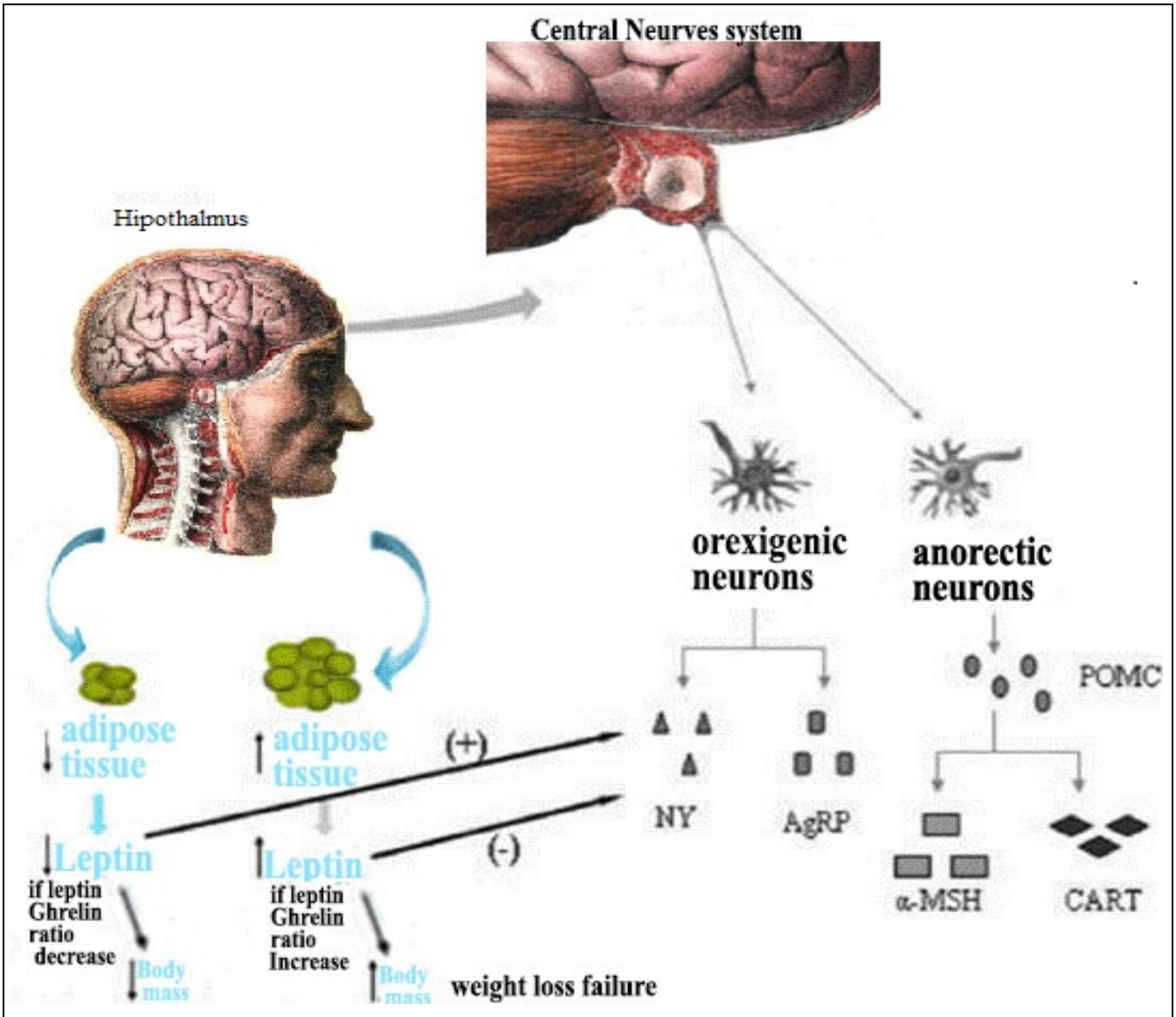

Figure 2. Mechanism of action of the Leptin hormone

Failure of leptin to act in obese individuals with resistance prevents the hormone from fulfilling its catabolic role. Under international standard I.S. conditions, it should be able to suppress feeding, resulting in decreased body weight and adiposity.

The aetiology of obesity is complex to identify because it is recognized as a multifactorial disease. Several factors are involved in its genesis, including genetic, psychological, metabolic, and environmental factors. It is known that adipocytes can synthesise various substances, and despite what was previously believed, adipose tissue is a storage site for triglycerides and an endocrine organ. Thus, understanding the mechanisms of hunger and satiety regulation, as well as the factors that interfere with them, is of substantial relevance because it can contribute to managing the disease.

Recent studies have focused on evaluating the factors influencing leptin levels, offering a better understanding of the subject and new treatment perspectives.

Adamska-Patruno et al. also observed the ratio of leptin to ghrelin during fasting in men of adequate weight and those overweight or obese [18,19]. The objective was also to recognise the possible changes in this leptin-to-ghrelin ratio when offered diets with different macronutrient compositions. The findings showed a notable difference in postprandial leptin and ghrelin levels between normal-weight individuals and the overweight/obese group. The results also suggested that individuals with adequate weight had a better satietogenic response when eating hyperglycemic meals, which was not observed in the overweight/obese group [18].

Leptin and Low carbohydrate intake

Ebbeling et al. (2020) observed that obese individuals had higher energy expenditure and a better result in maintaining weight loss when adopting a diet with a lower amount of carbohydrates [20]. For that, a study of 617 participants suggests that consuming low carbohydrates in diet may help weight loss [21].

Another study selected 30 obese adult women for interdisciplinary therapy to reduce body weight. A research done by Jamar et al. team identified that lower carbohydrate intake could influence and improve body composition and decrease leptin levels. In contrast, reducing fat intake also favoured weight loss and reduced inflammation and cardiovascular risk [22,23].

Effect of omega 3 and fatty acid

Payahoo et al. investigated the effects of n-3 polyunsaturated fatty acid (PUFA n-3) on leptin, satiety, and energy consumption in obese individuals [24]. The results showed that PUFA n-3 supplementation decreased the calorie intake of these individuals and provided a greater feeling of satiety during consumption [25]. However, the serum leptin levels did not undergo signifi-

cant changes, but a study by Balsevich et, al. Show that Free fatty acid increases leptin's hypophagic effects [26].

The Effect of ghrelin level and weight loss

Research published in the **Appetite** Journal regarding weight loss and the level of leptin and ghrelin pre and after-weight loss showed that higher levels of pre-weight-loss ghrelin might be associated with better odds of weight loss in individuals of both sexes. However, higher pre-weight-loss leptin to ghrelin ratio showed increased chances of weight loss failure in women [27]. Other interventions have also been evaluated as possible treatments for obesity and improvements in leptin function. Herrick et al., who studied the implications of physical exercise associated with food planning in obese individuals of both sexes, observed a reduction in adiposity and decreased circulating leptin levels, suggesting an improvement in leptin action [28]. Tremblay *et al.* sought to understand the long-term effects of high-intensity resistance and endurance exercises on ghrelin and leptin levels [29,30]. Their results showed that increasing exercise intensity with a diet based on dietary guidelines could potentiate fat loss before the individual reached a plateau in body weight. It was also observed that the beginning of the exercise program was marked by decreased leptin levels and increased ghrelin levels. However, in the months after the program, leptin levels remained stable, whereas ghrelin showed a reduction in plasma levels [29].

A study conducted on thin, overweight, and obese women, explored the effects of weight loss on serum leptin levels and the relationship between anthropometric measurements and leptin levels. The study found higher leptin levels in obese women, proportional to the anthropometric measurements. After 12 weeks of the weight-loss program, leptin levels were reduced in obese women [31].

Another recent study analysed the relationship between physical activity and inflammatory markers in child. It was observed that moderate-intense physical exercise improved the inflammatory profile of the participants [32]. However, the leptin levels did not change significantly.

Finally, a study analysing the influence of sleep and meal times on food intake and hormonal regulation of obese individuals showed that leptin levels were higher at normal meal times (the first meal in the morning and the last meal Before 00:00 (midnight) [33]. They also demonstrated that sleep times did not influence leptin levels. In contrast, Ghrelin levels were strongly influenced by sleep hours. This would suggest that sleep duration and meal performance may contribute to food choice and energy balance.

The results indicate that the most important approach is nutritional planning aimed at a calorie deficit accompanied by physical activity. Individuals with higher amounts of adipose tissue also had higher leptin levels [34-36].

Conclusion

In conclusion, higher levels of leptin pre-weight loss indicated a higher chance of weight loss failure, thus demonstrating an impairment in regulating energy balance in resistant individuals. Finally, some findings support the need for more studies investigating the influence of macronutrients on leptin levels and the influence of sleep and meal times. However, it was possible to recognise that leptin-resistant individual does not have efficient control of satiety, as observed in eutrophic individuals. Thus, it can be said that the disease is still through a multidisciplinary program involving food planning focused on calorie deficits and regular physical activity. As a possible limitation of the study, it is important to mention the variety in the sample of Obese individuals when comparing the various articles.

In some studies, only females were observed, whereas in others, only males were observed, and some studies observed both sexes.

Another relevant question concerns participant age because although all the study participants were adults, there is a considerable difference in the age groups that correspond to different life cycles.

Recent findings involving leptin produced by adipocytes demonstrate the need to create new fields of study for controlling and managing obesity, mainly involving the areas of nutrition and metabolism. Therefore, knowledge of these peptides is of great value in maintaining and preserving the population's quality of life and may boost the search for new therapeutic approaches to treating obesity.

this dysfunction of leptin favors the maintenance of obesity and hinders the weight-loss process.

As adiposity levels increase, there is excess leptin signaling in the hypothalamus, which consequently increases the concentration of inflammatory cytokines. This chronic inflammation results in the malfunction of leptin, which, despite being released in high amounts, is ineffective in controlling satiety.

Although studies seek promising pharmacological treatments or alternative behavioural and nutritional strategies, the best approach to treating

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Conflicts of interest The authors declare no conflict of interest.

Ethical approval

This study is a review article. There are no humans, animals, or data included in this article

Author contribution

Hany A. Alhussaniy draft the writing, supervision, and data analysis, proofread and edited the article, revise the article, decreased the bias, All the authors approved the submission of this manuscript.

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