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Serum Adipsin Levels in Obese and Normal Weight Adolescents with Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is a chronic and heterogeneous disease associated with obesity, hyperinsulinemia, dyslipidemia and chronic low-grade inflammation. Adipsin is a protein that is mostly secreted from adipose tissue and is a structural homolog of complement factor D, the rate-limiting enzyme of the alternative complement system. The aim of this study was to investigate adipsin levels in adolescents with PCOS and their relationship with obesity. 40 normal weight--children with PCOS and 40 obese-children with PCOS, and 40 normal weight healthy children participated in our study. Adipsin levels of adolescents in each group was measured in morning fasting blood samples by a commercial ELISA kit. Adipsin levels showed statistically significant differences between the groups ($p<0.001$). Normal-weight PCOS adolescents had higher adipsin levels than both obese PCOS and healthy controls. A negative correlation was observed between adipsin levels and BMI in the PCOS group ($r=-0,457$, $p<0,001$). In conclusion, adipsin can be considered as an independent risk factor in normal weight PCOS adolescents and may help in the diagnosis of PCOS in normal weight children with other symptoms.

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1. Introduction

Polycystic ovary syndrome (PCOS) is considered a chronic and heterogeneous disorder that usually manifests itself during adolescence and is seen in approximately 10-20% of adolescent and young adult women worldwide (Salhah et al., 2024; Siddiqui et al., 2022). PCOS is a condition characterized by the formation of cysts in the ovarian follicles as a result of hormonal changes and imbalances. The diagnosis of PCOS is based on the presence of multiple cysts in the ovary, and as the number of cysts increases, the condition of "polycystic ovary" (multi-cystic ovaries) occurs (Patel, 2018; Yang and Chen, 2024).

The pathogenesis of PCOS involves a complex interaction of genetic and environmental factors such as chemical exposure (Patel, 2018). Various hormone derangements are also seen in PCOS. Cycle duration and ultrasound (follicle count, mean ovarian volume) parameters, glucose tolerance test (GTT), prolactin test, endocrine and lipid profiles may indicate PCOS (Tsutsumi and Webster, 2009). However, insulin and congenital adrenal hyperplasia may direct the pathogenesis of PCOS. Abnormal course of androgen and estrogen hormones results in metabolic disorders such as overweight and obesity, diabetes, insulin resistance and hyperinsulinemia, infertility and disrupted menstrual cycle in PCOS patients (Chang et al., 2024; Patel, 2018; Yang & Chen, 2024). Cardiovascular diseases, psychological disorders, dyslipidemia, infertility and cancer are also associated with PCOS (Patel, 2018; Siddiqui et al., 2022). These pathophysiologies associated with PCOS are also associated with each other (Siddiqui et al., 2022).

DNA damage due to oxidative stress has been shown to be associated with ovarian carcinoma in women with PCOS (Siddiqui et al., 2022).

Some steps regarding the origins of the development of adolescent PCOS have been revealed. Decreased weight gain in the late prenatal period and increased weight gain in the early postnatal period create an imbalance between early subcutaneous fat formation and subsequent lipogenesis processes (Ibáñez & de Zegher, 2023). In particular, when sufficient lipid storage capacity is not developed in the early period, the body's increased lipid storage needs cannot be met, and this creates metabolic stress. In the second step, it is noteworthy that the body develops a response to ectopic fat in late childhood. In this process, the hormone dehydroepiandrosterone sulfate, whose levels increase in circulation, plays a role in the early onset and acceleration of pubertal processes, accelerating the maturation of girls. Activation of the gonadotropic axis accelerates sexual maturation, while changes in the thyroid axis increase metabolic rate and accelerate growth. All of these hormonal changes act as an adaptive response of the body to ectopic fat accumulation, resulting in accelerated growth and maturation. The third step is the cessation of growth in height as epiphyseal fusion occurs in the growth plates, and the effects of the body's adaptive response to ectopic fat by accelerating growth decrease. With the cessation of growth, the body's energy expenditure decreases, which may cause the excess energy to be stored as more ectopic fat.

During this process, the effects of the increase in levels of hormones such as LH, TSH, DHEAS and testosterone observed in the previous stages decrease, and these hormones tend to return to normal levels.

Adipose tissue has been described as an endocrine and inflammatory organ that secretes adipokines that affect systemic metabolism, stores energy, and secretes them when needed (Byeon et al., 2023; Scherer, 2019). Adipsin is an important adipokine secreted by adipocytes and is a protein that has an effect on the function of adipose tissue and cardiometabolic processes (Milek et al., 2022). Adipsin, first identified as *complement factor D* in 1987, is an enzyme belonging to the serine protease family and is expressed in both adipose cells and nervous system cells (Cook, 1985). Since adipsin is a protein produced by adipose tissue and released into circulation, it plays an important role in the homeostasis and energy metabolism of adipose tissue (Dare & Chen, 2024; Flier et al., 1987; Lo et al., 2014). Human studies have shown positive correlations between adipsin serum concentrations and BMI (Milek, 2022). The fact that adipsin levels are associated with age, body weight, body mass index (BMI), fasting plasma glucose, and leptin emphasizes the importance of adipsin in the pathophysiology of obesity, insulin resistance, and diabetes (Milek et al., 2022). High adipsin levels in prediabetic individuals suggest that adipsin can be used as a possible biomarker during this process when glucose metabolism deteriorations begin. This finding suggests that it may be important to monitor adipsin not only in individuals with Type 2 diabetes but also in prediabetic individuals at risk of developing diabetes.

High adipsin levels may be an indicator of early metabolic deteriorations such as inflammation, insulin resistance, and energy imbalance, and thus may provide better predictions about the risk of developing diabetes in patients with impaired glucose tolerance.

There are a few studies examining serum adipsin levels in women with PCOS. Our study will be the first study evaluaing adipsin levels in children diagnosed with PCOS during adolescence.

2. Materials and Methods

2.1. Study groups

The study included 40 over-weight adolescent with PCOS and 40 normal-weight adolescent with PCOS between the ages of 10-20 who applied to the Pediatric Endocrinology Polyclinic of Keçiören Training and Research Hospital (KAEH) and 40 healthy and normal weight female adolescent who applied to the Healthy Child Polyclinic.None of the controlsubjects or the PCOS patients had clinical or laboratory evidence of any disease that might have affected the parameters to be measured. The demographic parameters and laboratory results of PCOS patients and healthy controls are given in Table 1. The study was approved by the Ethical Committe of Gazi University Local ethics committee (dated 12.09.2022, ref.no:685). All the subjects were recruited on a voluntary basis. Children and their families were informed verbally and in writing about the details of the study before they were included in the study. Along with that, consent was obtained from both parents and children by signing an informed consent form. Hyperandrogenism, oligomenorrhea or amenorrhea associated with chronic anovulation, and polycystic

ovarian morphology are classic features of PCOS (Dumesic et al., 2015). The current consensus is that the Rotterdam criteria are appropriate for adult women. Women must meet two of three characteristics for a diagnosis of PCOS: oligo-ovulation or anovulation, clinical and/or biochemical hyperandrogenism, or polycystic ovarian morphology on ultrasound after exclusion of other disorders. However, it is difficult to define appropriate diagnostic criteria for PCOS in adolescent girls because irregular menstruation, cystic acne, mild hyperandrogenism, and multifollicular ovarian morphology, which can be seen in PCOS, can also occur during normal pubertal maturation, making the diagnosis of PCOS in adolescent girls difficult (Ib´añez et al., 2017; Teede et al., 2018; Witchel et al., 2015). Similar to the evaluation of adult women, disorders such as CAH associated with irregular menstruation and/or hyperandrogenism, typically nonclassical 21-hydroxylase deficiency, androgen-secreting tumors, thyroid dysfunction, hyperprolactinemia, Cushing's syndrome, exogenous use of steroid hormones/androgens, or severe IR syndrome need to be excluded. Patients who met the criteria after these exclusions were included in the PCOS group.

In children, instead of fixed BMI values as in adults, percentile curves prepared according to age and gender are used. Since there may be differences between ethnic groups, each country should use percentile curves prepared for its own children. Although BMI normograms prepared by the CDC (The Centers for Disease Control and Prevention) are available in the USA, BMI percentile values prepared by Olcay Neyzi and his colleagues are used for this purpose in our country (Neyzi et al, 2015).

A BMI below the 5th percentile for age and gender is defined as “underweight”, between the 5th and 85th percentile is defined as “normal weight”, between the 85th and 95th percentile is defined as “overweight”, above the 95th percentile is defined as “obese”, and above 120% of the 95th percentile value or a BMI of ≥35 kg/m^2 (whichever is lower) is defined as “severe obesity” (Kelly et al, 2013; Skinner et al, 2018). When classifying according to the standard deviation score (SDS), according to gender and age, if the BMI SDS is between -1 and 1, it is considered as "normal weight"; if it is between 1 and 2, it is considered as "overweight" and if it is ≥2, it is considered as "obese" (Flegal et al, 2009; Gulati et al, 2012).

Blood samples were taken from the children participating in the study after at least 8 hours fasting. The blood sample was centrifuged and the serum part was separated and stored at -20°C.

2.2. Experimental Measurements

The amounts of serum adipsin (Human ELISA kits, Elabscience, China) were determined with a commercial kit. In addition, all children's fasting blood triglyceride (TG), total cholesterol (TC), LDL-C, HDL-C, E2, LH, FSH, CRP, and insulin measurements were also made with routine laboratory tests.

2.3. Statistical analysis

The data obtained as a result of the study are indicated as the mean (standard deviation). Data analysis was

performed using IBM SPSS Statistics 22.0 software (IBM Corporation, Armonk, NY, USA). Whether the distributions of continuous variables were normal or not was determined by Kolmogorov-Smirnov test. Chi-square test was used for comparison of qualitative data in comparison of demographic data. The distribution of the variables was not normal so significance of differences between medians were estimated by Kruskal Wallis test for more than two independent groups. Spearman's rank correlation coefficient (r) was used to examine relationships between parameters. A P value <0.05 was considered significant.

3. Results

In the Kolmogorov-Smirnov test (significance level was taken as 0.05), the levels of laboratory parameters in our study did not show a normal distribution. For this reason, non-parametric tests were applied in the statistical analysis of the findings.

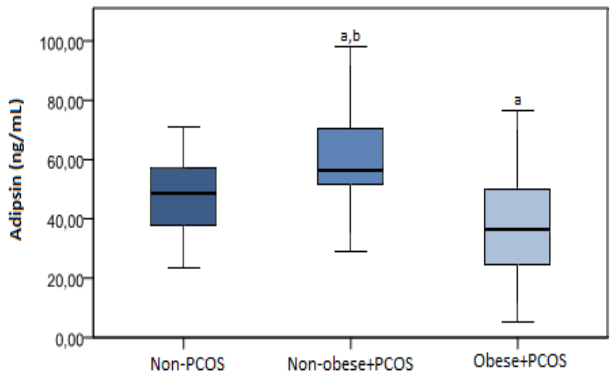
The study group was divided into 3 groups: over-weight adolescents with PCOS (obese+PCOS, n=40), normal-weight adolescents with PCOS (non-obese+PCOS n=40), and healthy controls of the same age group who did not have PCOS or any other disease (non-PCOS, n=40). The study groups were compared statistically according to age, BMI, family obesity status and family PCOS history, and the difference between some criteria was found statistically significant ($p<0.05$) (Table I). Also, HDL-Cholesterol, triglyceride, E2, FSH, LH, CRP and insulin levels showed a significant difference between groups ($p<0.05$) (Table I).

Table 1. Main characteristics of adolescents with PCOS and normal weight healthy controls

Variable	Obese + PCOS (N= 40)	Non-obese + PCOS (N= 40)	Non-PCOS (N=40)	P
Age, Mean (Standard Deviation)	15.5 (1.2)	14.8 (2.0)	14.5 (2.0)	0.046
BMI, Mean (Standard Deviation)	32.6 (4.4)	21.5 (3.0)	21.7 (3.8)	**0.001**
Family history of PCOS				
Yes, N (%)	8 (20.5)	10 (25)	1 (2.5)	**0.015**
No, N (%)	31 (79.5)	30 (75)	39 (97.5)	
Obesity status of the family				
Yes, N (%)	19 (47.5)	7 (17.5)	5 (12.5)	**0.001**
No, N (%)	21 (52.5)	33 (82.5)	35 (87.5)	
Laboratory Parameters				
Total Cholesterol (mg/dL)	161.2 (31.7)	176.4 (39.5)	164.5 (23.1)	0.235
LDL- Cholesterol (mg/dL)	91.3 (23.3)	101.6 (29.2)	101.5 (25.0)	0.216
HDL- Cholesterol (mg/dL)	45.9 (10.4)	50.8 (11.0)	50.5 (11.6)	**0.002**
Triglyceride, mg/dL	152.5 (112.8)	100.1 (46.5)	106.0 (47.8)	**0.020**
E2, pg/mL	60.6 (23.8)	81.8 (27.6)	109.5 (58.3)	**0.001**
FSH, mIU/mL	6.2 (3.1)	3.4 (3.9)	4.1 (2.1)	**0.001**
LH, IU/L	2.1 (1.7)	3.0 (3.2)	1.9 (1.1)	0.357
CRP, mg/dL	7.7 (2.0)	3.5 (2.3)	2.4 (3.0)	**0.001**
Insulin, mU/L	33.3 (30.8)	17.0 (16.6)	23.7 (8.3)	**0.001**
Adipsin, ng/mL	37.0 (17.7)	58.1 (18.3)	49.7 (16.4)	**0.001**

Table 1 also includes routine biochemistry tests of PCOS adolescents and healthy controls. Mean HDL-Cholesterol, triglyceride, E2, FSH, CRP and insulin levels were found to be significantly different between groups ($p<0.05$). Overweight adolescents with PCOS have higher triglyceride, FSH, CRP and insulin levels and lower HDL-Cholesterol and E2 levels than those in normal weight adolescents with PCOS and healthy controls ($p<0.05$).

Adipsin levels did not differ between total PCOS patients and healthy controls [47.0 (20.8) ng/mL vs. 49.7 (16.4) ng/mL, respectively] ($p>0.05$). When the PCOS group was divided into normal- and over-weight, adipsin levels showed statistically significant differences between the groups ($p<0.001$). Non-obese PCOS adolescents have statistically significantly higher adipsin levels than both obese PCOS adolescents and non-PCOS adolescents ($p<0.001$ and $p<0.05$, respectively) (Figure 1). At the same time, non-PCOS adolescents also have higher adipsin levels than obese PCOS adolescents ($p<0.05$)



[a] $p<0.05$ compared with non-PCOS,
[b] $p<0.001$ compared with obese-PCOS

Figure 1. Adipsin levels in PCOS and non-PCOS adolescents

When the relationships between adipsin levels and other parameters were examined in the total PCOS group, negative correlations were observed between adipsin and BMI, triglyceride, CRP and insulin (Table 2). In healthy controls, a positive correlation was observed between adipsin and LDL-cholesterol (Table 2).

Table 2. The relationship between adipsin and biochemical parameters in PCOS and non-PCOS adolescents

	Adipsin R (P)*	
	Non-PCOS	***PCOS***
BMI	-0.018 (NS)	**-0.457 (0.001)**
CHOLESTEROL	0.261 (NS)	0.151 (NS)
TRIGLYCERIDE	0.066 (NS)	**-0.260 (0.026)**
HDL	0.211 (NS)	0.103 (NS)
LDL	**0.468 (0.002)**	0.221 (NS)
E2	0.150 (NS)	0.131 (NS)
FSH	0.061 (NS)	-0.179 (NS)
LH	-0.045 (NS)	0.196 (NS)
CRP	-0.209 (NS)	**-0.378 (0.001)**
INSULIN	0.000 (NS)	**-0.302 (0.010)**

*R (P): Correlation coefficient (Significance)

4. Discussion

PCOS is reported to affect at least 1 in every 200 adolescent girls. Although the causes of PCOS development in adolescence are not fully known, some genetic and environmental factors that may create a predisposition have been identified (Saleh et al, 2024). It is thought that PCOS in childhood may show polygenic inheritance due to the influence of environmental factors. In addition, the increase in

inflammatory markers in PCOS suggests that inflammation may also be a factor, but it is not known whether it is directly involved in pathogenesis (Duleba & Dokras, 2012) A significant relationship has also been reported between obesity and the development of PCOS in children (Saleh et al., 2024) Both obese and normal weight children were included in our study.

Diagnosing PCOS in adolescence is difficult and controversial compared to adult women and based on two clinical entities: hyperandrogenism (clinical or biochemical) and menstrual irregularity. Adolescents with only one of these features can be considered "at risk" for PCOS (Burgert 2024). In recent decades, striking increases in the prevalence of overweight/obesity in girls have been accompanied by rapid maturation and marked increases in the prevalence of adolescent PCOS (Ibáñez & de Zegher, 2023). Adolescents with PCOS are observed to exhibit hyperandrogenism and insulin resistance (Siddiqui, 2022). The main diagnostic criteria for adolescent PCOS are hirsutism, acne, seborrhea, androgen excess in girls, and oligo-amenorrhea (>2 years after menarche) (Ibáñez & de Zegher, 2023; Zegher et al., 2018).

Adipsin, also known as complement factor D, is a protease with a cytokine structure and provides the relationship between adipose tissue metabolism and complement pathways. The fact that adipsin levels are associated with age, body weight, BMI, fasting plasma glucose, and leptin emphasizes the importance of adipsin in the pathophysiology of obesity, insulin resistance, and diabetes (Chedraui et al.,2014; Milek et al., 2022). Adipsin, first identified as complement factor D, also activates the alternative complement pathway and is therefore an important component of the immune system (Cook, 1985; White et al., 1992). The complement system is a part of the innate immune system and has been shown to be linked to inflammation, obesity, insulin resistance and cardiovascular disease (Hertle et al., 2012). Because of some evidence that there is a connection between the complement system and PCOS, it has been thought that adipsin may play a role in PCOS. In our study, adipsin levels were significantly higher in adolescents with PCOS than in healthy controls. However, although adipsin is a protein secreted from adipocytes, its levels were lower in obese adolescents with PCOS than in those with normal weight. This result was also confirmed by the correlation test, and a significant negative correlations were observed between BMI and adipsin and between triglyceride and adipsin in the PCOS group. In previous studies, it has also been shown in preclinical studies that adipsin levels are reduced in different animal models of obesity, (Cook et al., 1987), but human studies have found positive correlations between adipsin serum concentrations and BMI (Milek, 2022). In a recent study, similar to our results, adipsin levels found to be decreased in obese females with PCOS than those in lean females with PCOS (Tanilir Çağiran & Kali, 2024; Vejrazkova et al., 2017). In two different studies, adipsin levels were found to be higher in overweight women with PCOS than in lean women (Butler et al., 2022; Gürsoy Calan et al., 2016). However, Butler et al. found a positive correlation between BMI and complement factor D.

5. Conclusion

Confusing results have been obtained regarding adipsin levels in different diseases and conditions. Although significantly higher adipsin levels were observed in normal weight PCOS in our study, it was not found to be associated with other parameters of this disease. Since evaluations regarding adipsin levels are generally made based on adult levels, it can be considered that adipsin levels may be affected by different mechanisms in adolescents where hormonal balance is restructured. On the other hand, adipsin can be considered as an independent risk factor in normal weight PCOS adolescents and may help in the diagnosis of PCOS in normal weight children with other symptoms.

Ethics Committee Approval

The study protocol was approved by the Ethical Committe of Gazi University (dated 12.09.2022, ref.no:685)

Conflict of Interest

No conflict of interest was declared by the authors.

Authorship Contributions

Concept: ÇE, SYA, Design: ÇE, SYA, ADB, Data Collection or Processing: ÇE, ADB, YY, Analysis or Interpretation: SYA, ÇE, ADB, YY, Literature Search: ÇE, SYA, YY Writing: SYA, ÇE, ADB, YY

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Research Article

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Bibliometric Analysis of Post-Covid-19 Rehabilitation Research

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musculoskeletal recovery,
cognitive dysfunction,
fatigue management

Abstract

The long-term effects of the COVID-19 pandemic have adversely impacted individuals' physical and psychosocial health, creating new research areas in rehabilitation. A comprehensive review of post-COVID-19 rehabilitation literature is essential to understand the current state of the field and identify future research priorities.

This study aims to conduct a bibliometric analysis of the literature on post-COVID-19 rehabilitation to evaluate the development of research areas and trends. Articles and related publications indexed in the Web of Science database until December 10, 2024, were reviewed. Using relevant keywords, 81 publications were identified and analyzed bibliometrically. Descriptive statistics were performed using IBM SPSS 22.0, and collaboration networks of authors, keyword co-occurrence relationships, and citation connections were visualized using VOSviewer software. The analysis revealed a significant increase in publications on post-COVID-19 rehabilitation, particularly in 2023. Pulmonary rehabilitation, musculoskeletal recovery, fatigue management, and cognitive dysfunction emerged as key research areas. Keywords such as "Covid-19," "Rehabilitation," and "Pulmonary Rehabilitation" were the most frequently used. Collaboration network analysis highlighted the United Kingdom, the United States, and Italy as central contributors.

The findings suggest that post-COVID-19 rehabilitation has become a multidisciplinary research focus, addressing neurological and psychological effects alongside fatigue and cognitive rehabilitation. Future studies should focus on cellular mechanisms and long-term clinical outcomes to enhance the effectiveness of rehabilitation programs.

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1. Introduction

The COVID-19 pandemic has become a crisis that significantly challenges healthcare systems worldwide, not only during the acute phase but also due to its long-term effects (World Health Organization, 2021). Post-acute manifestations, known as long COVID or post-COVID syndrome, present a complex array of both physical and psychosocial complications (Nalbandian et al., 2021). These complications range from musculoskeletal disorders and reduced respiratory function to fatigue syndrome and cognitive dysfunction. Consequently, the long-term impacts of COVID-19 have necessitated the development of new approaches in the field of rehabilitation medicine (Greenhalgh et al., 2020).

Post-COVID-19 rehabilitation has emerged as a crucial area of focus, aiming to restore functionality and enhance the quality of life for individuals during and after the pandemic (Chen et al., 2021). The literature in this domain has rapidly expanded, with researchers from various disciplines contributing significantly (Sivan & Taylor, 2020). However, systematically analyzing this growing body of work is essential to understand the current state of the field, and bibliometric approaches play a critical role in this endeavor.

This study aims to present a bibliometric analysis of the post-COVID-19 rehabilitation literature. By examining authorship, country of origin, journals, keywords, and citation trends, the research seeks to identify key developments and areas for growth within the field. We believe that the findings will guide academic endeavors and inform future practices in post-COVID-19 rehabilitation.

2. Material and Methods

The study included articles, reviews, and other relevant publications indexed in the Web of Science (WoS) database up to December 10, 2024. A bibliometric analysis was conducted on 81 publications retrieved using the following keywords: ("Post-COVID-19 rehabilitation" OR "Long COVID rehabilitation" OR "Post-acute COVID-19 rehabilitation" OR "COVID-19 recovery rehabilitation" OR "COVID-19 sequelae treatment" OR "COVID-19 physical therapy" OR "COVID-19 physiotherapy" OR "COVID-19 rehabilitation outcomes") (Topic). The analysis focused on co-authorship among authors, co-occurrence of keywords, and co-authorship among countries. Descriptive statistics of the bibliometric data were analyzed using IBM SPSS 22.0 (SPSS Inc., Chicago, USA). Key metrics such as publication trends, citation counts, influential countries, and journals were examined. Author collaboration networks, keyword co-occurrence relationships, and citation links were visualized using VOSviewer 1.6.16 software.

Data preprocessing, visualization, and clustering were performed using VOSviewer 1.6.16. Co-authorship among authors, co-occurrence of keywords, and co-authorship among countries were evaluated with VOSviewer. Total Link Strength (TLS) reflects the overall connection weight by indicating the total links of a node (e.g., a country, author, or journal) with other nodes and the significance of these links. In this study, TLS values were used to assess collaborations between countries, joint works among authors, and connections between journals. Nodes with high TLS values demonstrate significant contributions to the

academic network through strong collaborative links with other nodes.

The obtained data were examined based on authors, journals, countries, and keywords. Descriptive statistics were generated using SPSS 25, and categorical data were presented as counts and percentages.

Since bibliometric studies are conducted on open data, they do not require ethical committee approval (Levin et al., 2023). As the data used in this study are publicly available, ethical committee approval was not sought.

3. Results

When examining the distribution of publications by year, it was observed that 7 studies (8.6%) were published in 2020, 16 studies (19.8%) each in 2021 and 2022, reaching the highest number in 2023 with 24 studies (29.6%). The number of publications for 2024 was determined to be 18 (22.2%).

In terms of document types, articles accounted for the highest proportion at 76.5% (n=62), followed by conference abstracts at 12.3% (n=10), editorial writings and reviews at 4.9% (n=4), and letters at 1.2% (n=1).

Regarding language distribution, English was the most common at 96.3% (n=78), with Spanish at 2.5% (n=2) and Portuguese at 1.2% (n=1).

Only four journals had more than three publications, all indexed in the "Science Citation Index-Expanded." The distribution is as follows: "Journal of Clinical Medicine" with 6 publications (7.4%), "BMJ Open" with 4 publications (4.9%), "European Respiratory Journal" with 4 publications (4.9%), and "International Journal of Environmental Research and Public Health" with 3 publications (3.7%).

In terms of citations, the average number of citations per study was calculated as 13.1±48.6, with a median of 2. The citation range varied between 0 and 428, with 34.6% of the studies not receiving any citations.

4. Author Collaboration

In this section, the relationships and interactions among 599 authors collaborating in a specific area across 81 publications are analyzed and visualized. In the analysis conducted using VOSviewer, the criterion of having at least one document was applied; however, not all authors were connected to each other. The 51 authors with the highest collaboration or relationship were visualized, while those unrelated were excluded. The 4 identified clusters enhance the precision and effectiveness of the results. These clusters represent the connections among authors (Figure 1).

"Total link strength" reflects the overall link weight and importance of a node with others in the network. The authors with the strongest total link strength are as follows: Brown, Darren A. (37 link strength, 3 publications, 24 citations), Gross, Douglas P. (26 link strength, 2 publications, 24 citations), O'Brien, Kelly K. (21 link strength, 2 publications, 21 citations), Tarrant, Rachel (19 link strength, 2 publications, 29 citations), O'Connor, Rory J. (17 link strength, 2 publications, 67 citations), Preston, Nick (17 link strength, 2 publications, 67 citations), and Sivan, Manoj (17 link strength, 2 publications, 67 citations). These authors stand out both in terms of their link strength within the collaboration network and their number of publications and citations.

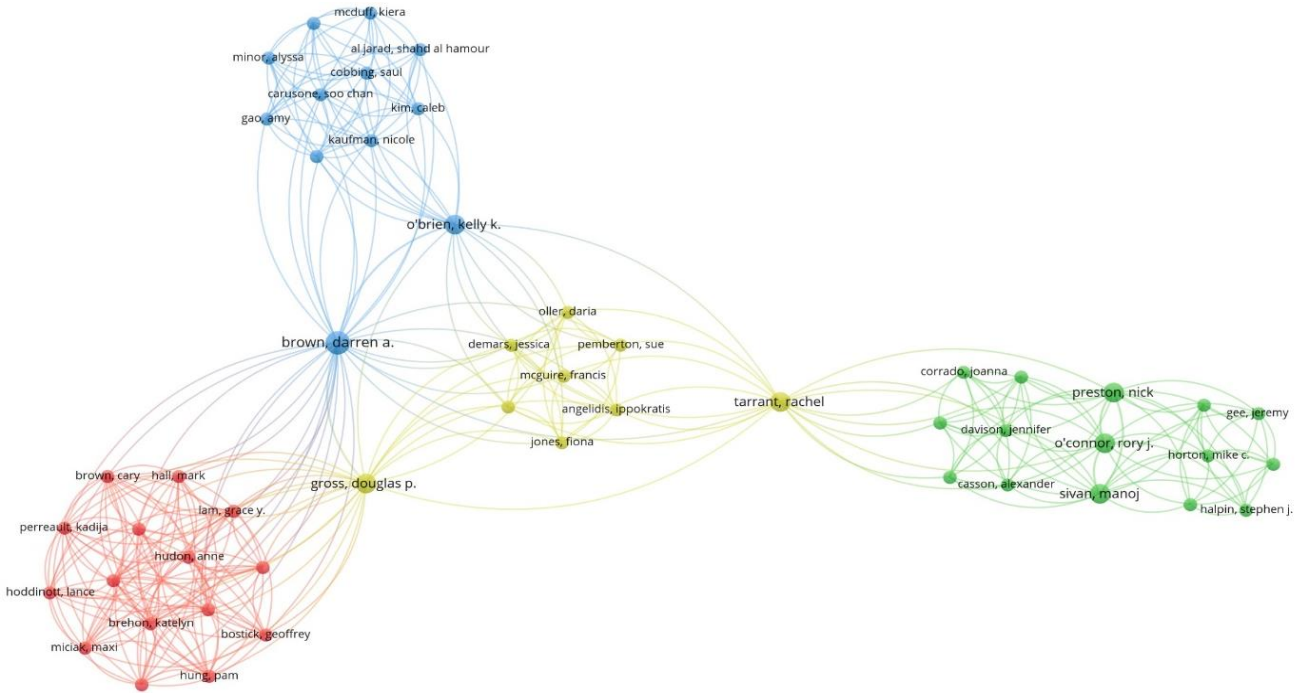

Figure 1. Collaboration Network Among Authors. (The network includes a total of 599 authors; however, some of them are not connected to each other. The 51 authors with the highest collaboration or relationships have been visualized, while unconnected authors are not shown).

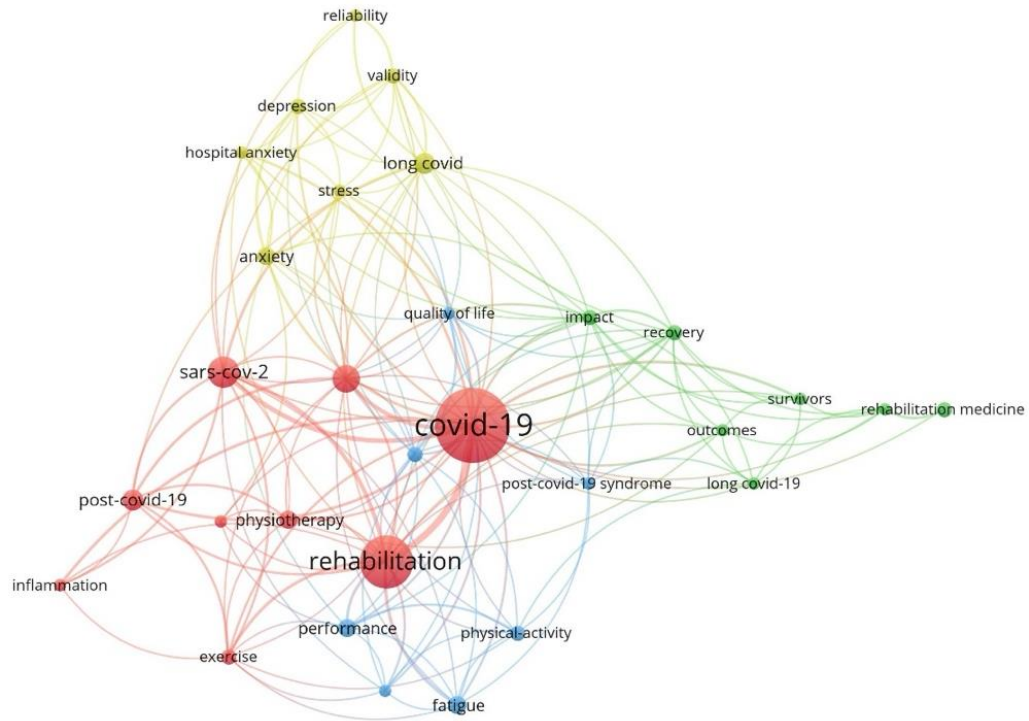

Figure 2. Keyword Network Analysis

5. Keyword Analysis: Co-occurrence Network Analysis

In this section, a "Co-occurrence Keywords" analysis was conducted to examine how frequently the keywords used in the publications appear together. According to the analysis results, a total of 351 keywords were identified across 81 publications, and these keywords were divided into 4 different clusters based on their co-occurrence and relationships with each other (Figures 2). These clusters represent keywords that are frequently used together around a specific topic, method, or research area. To be included in the analysis, a keyword had to appear at least 3 times, and out of the total 351 keywords, only 30 met this criterion (minimum 3 occurrences).

The total link strength indicates how frequently a keyword appears together with other keywords. A high total link strength value signifies that the keyword has a strong relationship with other keywords. In the keyword co-occurrence analysis, the most frequently used keywords with the highest total link strength are as follows: Covid-19 (39 occurrences, 79 link strength) and Rehabilitation (24 occurrences, 52 link strength) emerged as the most commonly used keywords. These were followed by SARS-CoV-2 (11 occurrences, 33 link strength) and Pulmonary Rehabilitation (9 occurrences, 27 link strength).

Other significant keywords include Long Covid (6 occurrences, 18 link strength), Anxiety (5 occurrences, 17 link strength), Exercise (4 occurrences, 17 link strength), and Post-COVID-19 (6 occurrences, 16 link strength).

6. International Collaboration Network

The Co-authorship by Countries analysis was conducted to examine and visualize the relationships between countries of authors collaborating on documents published in a specific field. Using VOSviewer, 41 countries with at least one publication were included in the analysis. However, due to some countries remaining independent in the network, only 23 countries were included in the geographic distribution graph. Countries such as the United Kingdom, Italy, and the United States are central to the network both in terms of collaborations and citation counts (Figure 3).

Based on total link strength, the collaboration between countries is as follows: the United Kingdom (20 link strength, 18 publications, 567 citations) holds the highest link strength. This is followed by Italy (12 link strength, 7 publications, 127 citations), Switzerland (11 link strength, 3 publications, 47 citations), and the United States (11 link strength, 10 publications, 90 citations). Spain (10 link strength, 6 publications, 90 citations), Germany (9 link strength, 5 publications, 33 citations), and the Netherlands (8 link strength, 2 publications, 19 citations) are also among the significant countries.

These countries occupy a central position in the collaboration network, making substantial contributions in terms of publication counts and citation values.

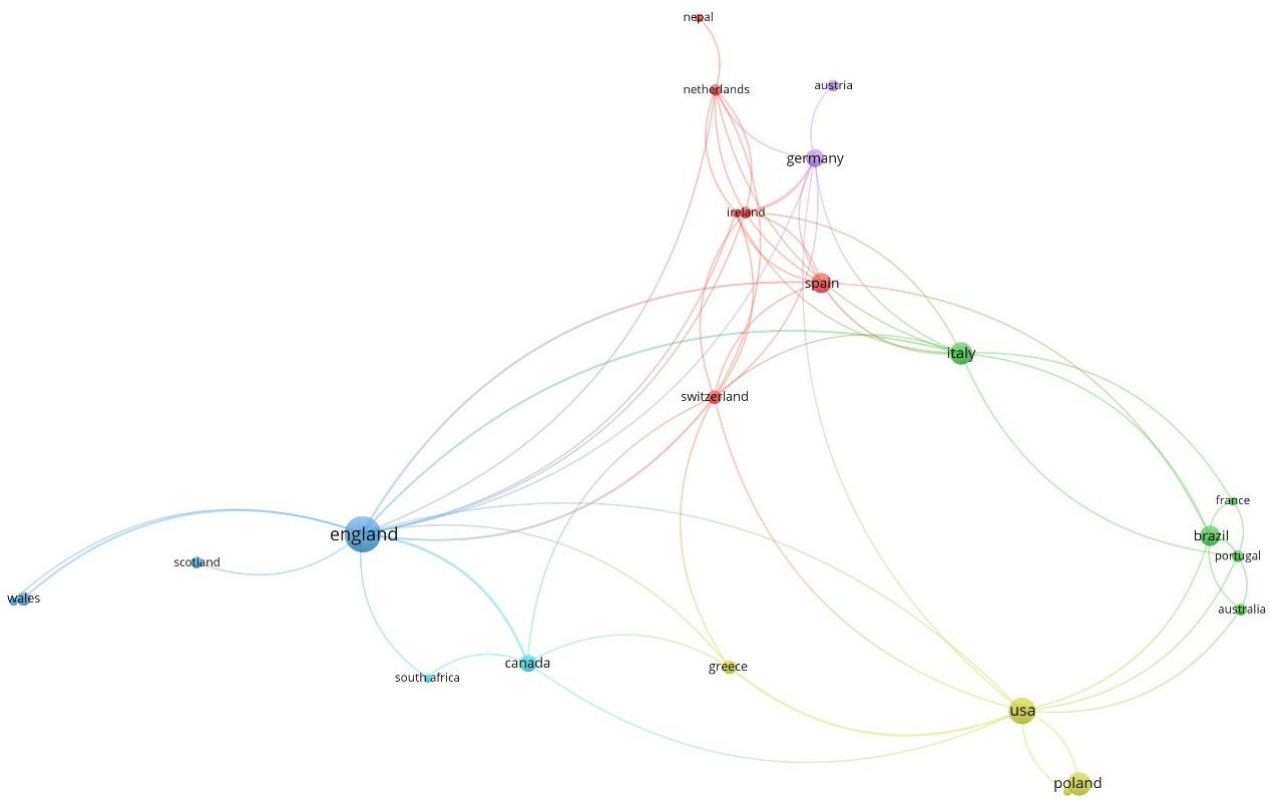

Figure 3. Collaboration Network Among Countries

7. Discussion

This study objectively presents a comprehensive bibliometric analysis of the literature on post-COVID-19 rehabilitation. Insights have been obtained that can guide researchers and healthcare professionals to predict the future development of this field. Additionally, through analyses of co-authorship among authors, co-occurrence of keywords, and co-authorship among countries, the overall structure and interaction network of this field have been examined in detail.

The key topics highlighted in studies on post-COVID-19 rehabilitation focus on accelerating recovery processes after the pandemic and improving quality of life. The bibliometric findings show that there is intense global collaboration in this field, with contributions from researchers across multiple disciplines. For instance, studies aimed at improving lung functions emphasize the importance of pulmonary rehabilitation in this process. Furthermore, topics such as the effects on the musculoskeletal system and fatigue management have also become primary focal points of rehabilitation programs (Huang et al., 2021).

The results of the keyword analysis indicate that the most frequently used terms in the post-COVID-19 rehabilitation literature are "Covid-19" and "Rehabilitation." These are followed by "SARS-CoV-2" and "Pulmonary Rehabilitation." These findings support the prominence of respiratory rehabilitation and physical recovery processes as key topics in the literature. Additionally, the use of keywords such as

"long COVID" and "post-COVID-19" highlights the focus on managing chronic symptoms and investigating long-term effects as current research priorities. This provides an essential foundation for understanding the current dynamics and future research opportunities in the field (Xue et al., 2022). The trends in post-COVID-19 rehabilitation indicate increasing interest in this topic, supported by a steady rise in the number of published studies. Current data reveal that reports are frequently published on the significant role of COVID-19 rehabilitation in improving both respiratory functions and physical capacity. In particular, the widespread findings on the safety and effectiveness of rehabilitation point to its potential to make greater contributions to future research. Trend lines obtained from bibliometric analyses show that intensive knowledge production in this research area will continue, and new findings will be added to the literature (Sivan et al., 2020).

Among the journals with the highest number of publications, Journal of Clinical Medicine ranks first in terms of impact factor (IF), CiteScore, and citation frequency. The journal's category is medicine, with a subcategory of general clinical medicine; its ranking places it among high-impact journals in this field. This indicates that academic articles published in this journal are of high quality and possess a strong impact. In terms of publishing countries, the journal originates from the United Kingdom, suggesting that the UK has invested more in this field and placed greater importance on it.

The analysis of the strongest citation bursts helps to predict research trends and boundaries in the field of post-COVID-19 rehabilitation. In the early periods (2020–2021), the prominence of keywords such as respiratory function and pulmonary rehabilitation indicates a focus on addressing the acute respiratory system effects of COVID-19. In the mid-term period (2022–2023), the increased use of terms like long COVID, mental health, and neurological rehabilitation reveals a tendency to explore the long-term neurological and psychosocial effects of COVID-19. In recent years, concepts such as cognitive dysfunction, fatigue management, and physical activity have become central research focuses, emphasizing the importance of comprehensive and multidisciplinary interventions in post-COVID-19 rehabilitation processes. These trends suggest that future studies will focus on innovative strategies aimed at mitigating the long-term effects of COVID-19.

These trends indicate that post-COVID-19 rehabilitation has become an important research focus regarding the management of diseases associated with chronic effects and applications aimed at improving quality of life. In the future, detailed studies on cellular and molecular mechanisms are anticipated to be one of the significant areas of development in this field. For example, some studies have shown that interventions enhancing neuroplasticity are effective in post-COVID-19 rehabilitation. Additionally, recent studies have found that physical exercise provides positive effects on the musculoskeletal system damaged by COVID-19 and activates cell repair mechanisms to alleviate chronic fatigue syndrome (Spruit et al., 2020; Fathi & Rezaei, 2020).

These findings suggest that further research into the biological foundations of post-COVID-19

rehabilitation will be conducted, and new discoveries in this area will enhance the effectiveness of rehabilitation programs.

In this bibliometric and visualization analysis, we focus on non-invasive and effective interventions, which are an important research topic in post-COVID-19 rehabilitation. The initial studies on post-COVID-19 rehabilitation began to be published in 2020, following the acute effects of the pandemic. In these early studies, pulmonary rehabilitation and musculoskeletal effects were particularly prominent (Spruit et al.,2020). The effects of physical interventions aimed at improving respiratory functions and the efficacy of exercise programs were extensively examined during this period (Greenhalgh et al.,2020).

In recent years, research on topics such as cognitive dysfunction, fatigue management, and neurological rehabilitation has rapidly increased. For example, some studies have reported that physical exercises improve neurological and musculoskeletal damage caused by COVID-19 (Nalbandian et al., 2021). However, research on the long-term effects of COVID-19 has also revealed some conflicting results. Specifically, it has been reported that certain interventions do not increase respiratory capacity or have limited effects on physical performance (Carvalho-Schneider et al., 2021). Conversely, the positive effects of psychosocial support and multidisciplinary rehabilitation programs on patients' quality of life have been repeatedly emphasized (Sivan & Taylor, 2020).

This study has certain limitations. First, only the Web of Science database was used in this research, and other databases were excluded; therefore, some relevant articles may have been missed. However, based on the published literature, Web of Science is the most widely used database in bibliometric analyses (Suelzer et al., 2019; Sugimoto et al., 2019). Web of Science contains a significant portion of the literature in this field and offers a broad enough scope to reflect research trends and perspectives in post-COVID-19 rehabilitation treatment.

Second, the literature in the database is continuously updated, but we selected only articles published between 2020 and 2024, excluding studies that may be published in 2025. Finally, this analysis is a timeline-based bibliometric analysis. Therefore, high-quality articles published in recent years may not have received sufficient citations yet and could potentially be undervalued.

Based on these limitations, researchers should conduct a comprehensive review of the relevant literature to gain a deeper understanding of the field.

8. Conclusion

This study comprehensively examined the literature on post-COVID-19 rehabilitation, highlighting current research trends and future potential research areas. According to the results of the bibliometric analysis, post-COVID-19 rehabilitation studies focus on topics such as improving respiratory functions, musculoskeletal rehabilitation, fatigue management, and cognitive dysfunction. In recent years, this field has emerged as an area of research where multidisciplinary approaches are increasingly prominent.

The long-term effects of COVID-19 are not limited to the respiratory system but also include neurological, psychological, and physical issues. This underscores the importance of developing customized rehabilitation programs tailored to individual needs. To enhance the effectiveness of rehabilitation interventions, more in-depth studies focusing on both clinical applications and cellular and molecular mechanisms are needed.

The findings indicate that post-COVID-19 rehabilitation holds significant potential for future research, particularly in areas such as neuroplasticity, cellular repair mechanisms, and multidisciplinary approaches. High-quality, long-term studies in this field will enhance the effectiveness of rehabilitation programs and contribute to the development of new strategies aimed at improving the quality of life for post-COVID-19 patients.

Ethical Statement

This study is a bibliometric analysis and does not require ethical approval.

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Presentation Information

The findings of this study have not been presented at any conference or meeting prior to this publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding this study. Any institution or organization providing funding for this research did not have any role in the design, data collection, analysis, interpretation, or publication to influence or distort the findings.

Author Contributions

All stages of this study (study design, data collection, analysis, interpretation, writing, and editing) were conducted by a single author. The full responsibility for the study rests with the author. Author: Özlem Karataş

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Review

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The Potential of MIND Diet to Improve Brain Health for American Football Players

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Abstract

Since American football is inherently a collision sport, exposure to repeated head impacts leads to increased concerns among players, especially regarding brain health. The risk of neurodegenerative diseases may rise at the later phase of life in case of the long-term continuation of brain damage induced by repetitive head impacts thereby leading to the chronicity of oxidative stress and neuroinflammation along with the blood-brain barrier disruption. Therefore, early preventive strategies are necessary to improve brain health. Nutrition is considered one of these strategies. The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet model was designed to improve brain health. The MIND diet includes foods rich in bioactive compounds, fiber, polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs) with anti-inflammatory and antioxidant characteristics. Therefore, this diet model may protect the brain against the negative effects of brain damage. The potential effects of MIND diet components, including bioactive compounds, fiber, PUFAs, and MUFAs on brain health for American football players are discussed in this review.

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1. Introduction

Participation in popular and now globally played American football has been reported to decline in recent years because of increasing concerns about brain health (Cecchi et al., 2021; Stone et al., 2019). In particular, this collision sport carries a high risk of exposure to repeated head impacts and, therefore, brain damage (Marchi et al., 2013). The likelihood of being exposed to head impacts increases as the level of experience increases in American football (Choi et al., 2022). It is stated that American football players are more likely to develop neurological conditions in old age, including amyotrophic lateral sclerosis, Alzheimer's disease, and chronic traumatic encephalopathy (Hampshire et al., 2013; Kochsiek et al., 2021; Lehman et al., 2012).

The underlying reasons for the neurodegenerative diseases seen in American football players have been considered to be long-term exposure to brain damage induced by repetitive head impacts and the resulting symptomatic brain injuries such as subconcussive injuries and concussions (Kochsiek et al., 2021). Brain damage can lead to neuronal damage, increased reactive oxygen species (ROS), and proinflammatory cytokines (signalling molecules) along with an impaired blood-brain barrier (BBB), a key cellular barrier tightly controlling the microenvironment of the central nervous system (CNS) to support balanced neuronal function (Daneman & Prat, 2015; Kim et al., 2022). Exposure to long-term and severe brain damage or resulting concussion can lead to chronic oxidative stress and neuroinflammation, which, if sustained, can subsequently trigger neurodegenerative progression (Hoffman et al., 2022; Kochsiek et al., 2021).

It is thought that the risk of developing neurodegenerative disorders may be reduced by decreasing the negative effects of brain damage (Hoffman et al., 2022; Oliver et al., 2016; Zuckerman et al., 2018). Therefore, strategies to improve brain damage-induced inflammation and oxidative stress are crucial in the early stage of life (Churchill et al., 2017; Walrand et al., 2021). Lifestyle factors, such as dietary habits, can be considered as one of the strategies to support brain health in American football players (Walton et al., 2021). Consumption of processed foods deficient in nutrients can compromise the brain's resilience and flexibility and increase inflammation and oxidative stress owing to brain damage (Fesharaki-Zadeh, 2022; Mullins et al., 2022; Walrand et al., 2021). On the other hand, a diet model like the MIND diet, which includes foods rich in bioactive compounds and nutrients such as fiber, PUFAs, and MUFAs with antioxidant and anti-inflammatory properties, may improve brain health (Oliver et al., 2016; Walrand et al., 2021). Therefore, this paper will discuss the potential effects of MIND diet components including bioactive compounds, fiber, PUFAs, and MUFAs on brain health for American football.

2. MIND Diet

The MIND diet emphasizes limiting the consumption of cheese, red meat, butter, sweets, and fried foods and increasing the intake of berries, fish, green leafy vegetables, olive oil, whole grains, nuts, beans, and poultry (Morris et al., 2015). The MIND diet is designed by Morris et al. (2015) to improve certain dietary factors after the Mediterranean and DASH

diets and to provide the maximum beneficial impact on brain health (Barnes et al., 2023).

The MIND diet's anti-inflammatory and antioxidant features are mostly elevated by preferred foods such as whole grain products, beans, green leafy vegetables, fish, olive oil and berries which are the source of bioactive compounds and key nutrients such as fiber, MUFAs, and PUFAs (Barnes et al., 2023). Drinking a glass of wine per day is also recommended. Wine is a drink rich in bioactive compounds. The MIND diet includes foods with these important components which may provide neuroprotective benefits (Barnes et al., 2023; Morris et al., 2015).

The following sections will elaborate on the potential effects of MIND diet components, such as bioactive compounds, fiber, PUFAs, and MUFAs on brain health.

2.1. Bioactive compounds

Bioactive compounds are substances that have physiological and biological activities. Moreover, these substances also provide health benefits over the main nutritional value of a food (Guaadaoui et al., 2014). The MIND diet provides bioactive compounds like phenolic substances including terpenoids (carotenoids and phytosterols), glucosinolates, alkaloids, and polyphenols through recommended foods such as green leafy vegetables, beans, and whole grains, besides olive oil and wine (Sorrenti et al., 2023).

Studies usually attribute the positive effects of bioactive compounds on brain health to their anti-inflammatory and antioxidant abilities thereby neuroprotective potentials.

The presence of bioactive compounds can reduce brain damage-induced ROS and proinflammatory cytokines (Kim et al., 2022). Therefore, they prevent the increase of oxidative stress and neuroinflammation and support the recovery of disrupted microglia including the plentiful inhabitant macrophages in the CNS, responsible for tissue defence and repair (Zaa etl al., 2023). Among bioactive compounds, polyphenols stand out with their strong anti-inflammatory and antioxidant capabilities (Kim et al., 2022). Foods such as green leafy vegetables, berries, and wine included in the MIND diet have abundant flavonoids and resveratrol, which are considered some of the polyphenols most researched for their potential beneficial effects on brain health (Ardekani et al., 2023; Caruana et al., 2016; Chaves et al., 2018). Some of the important polyphenols frequently found in foods included in the MIND diet are summarized in Table 1 (Manach et al., 2004).

As for flavonoids, catechin, epicatechin, and epigallocatechin-3-gallate have been shown to implement neuroprotective effects on the neurons encompassing the injured area of the brain by hindering apoptotic cell death. Besides, they can decrease the expression levels of the mRNA of proinflammatory factors like interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and inducible nitric oxide synthase (iNOS) (Carecho et al., 2023). Anthocyanins can contribute to the protection from oxidative stress and apoptosis of neurons. The protective activities of anthocyanins are relatively because of their ability to trigger Nrf-2 transcription factor activation which binds to the main antioxidant response regulator (Nrf-2/antioxidant response). For example, the berries' anthocyanin cyanidin-3-glucoside induces the Nrf-2 antioxidant defence

system causing a fall of oxidative stress and apoptosis within stressed cultured neurons (Zaa et al., 2023). Anthocyanins also attenuate inflammatory stress signalling via the inhibition of the nuclear factor kappa B (NF-κB) pathway giving rise to neuroinflammation, neuronal dysfunction and cell death by generating proinflammatory molecules such as TNF-α, interleukin 1 beta (IL-1β), iNOS, and ROS. Therefore they support the survival of microglial cells (Henriques et al., 2020). Luteolin has also been reported to alleviate inflammation after brain damage by decreasing IL-1 and TNF-α levels, and restoring anti-inflammatory factors such as glutathione peroxidase (GPx) activity. Apart from these, resveratrol is a non-flavonoid polyphenol abundant in wine. It may lead to decreased microglia activation with its antioxidant and anti-inflammatory properties after brain damage. In terms of the inflammation and oxidative stress-reducing capability, it has been reported that resveratrol reduces ROS, malondialdehyde, 8-hydroxy-20-deoxyguanosine protein, IL-1, IL-6, IL-12, and TNF- α, while increasing the GPx activity and IL-10 levels and improving NF-κB pathway in the affected brain tissue (Nath et al., 2022).

The bioactive compounds included in the MIND diet may help to improve brain damage, with their antioxidant and anti-inflammatory characteristics. The ability of polyphenols to interplay with various physiological processes makes them promising bioactive compounds to support brain health.

Table 1. Some of the important polyphenols frequently found in foods included in the MIND diet (Adapted from Manach et al., 2004)

Polyphenols	Food sources/serving size	Polyphenol content (mg/serving)
Anthocyanins (Cyanidin, Pelargonidin, Peonidin, Delphinidin, Malvidin)	Blackberry/100 g	100-400
	Blueberry/100 g	25-500
	Strawberry/200 g	30-150
	Red wine/100 mL	20-35
Flavonols (Quercetin, Kaempferol, Myricetin)	Curly kale/200 g	60-120
	Blueberry/100 g	3-16
	Beans, green or white/200 g	2-10
	Red wine/100 mL	0,2-3
Flavones (Apigenin, Luteolin)	Parsley/5 g	1,2-9,2
Isoflavones (Daidzein, Genistein, Glycitein)	Soybeans, boiled/200 g	40–180
Monomeric flavanols (Catechin, Epicatechin)	Beans/200 g	70–110
	Blackberry/100 g	13
	Red wine/100 mL	8–30

2.2. Dietary Fiber

Sports-related acute to chronic brain trauma induced by brain damage or repetitive head impacts can lead to gastrointestinal dysfunction by increasing intestinal permeability (Al-Ayadhi et al., 2021; Ramezani Ahmadi et al., 2020; Tillisch et al., 2013; Walrand et al., 2021). Although the exact mechanism is unknown, it is stated that brain trauma stimulates the sympathetic adrenal medullary system, leading to contraction of the gastrointestinal blood vessels, decreased blood flow, inadequate perfusion of the gastrointestinal tissue and circulatory ischemic hypoxia in the intestine (Guangliang et al., 2024; Iftikhar et al., 2020). In addition, excessive activation of the hypothalamic-pituitary-adrenal axis (HPA) and autonomic nervous system leads to partial loss of intestinal neurons (Li et al., 2020). It is thought that increased intestinal microvascular permeability due to these factors leads to disruption of the gastrointestinal mucosal barrier (Guangliang et al., 2024; Iftikhar et al., 2020; Li et al., 2020). The damaged gastrointestinal tract adversely modifies gut microbiota (the living microorganisms found in a defined environment) homeostasis leading to bacterial imbalance, called dysbiosis, which, in turn, may affect neural pathways (Al-Ayadhi et al., 2021; Ramezani Ahmadi et al., 2020; Tillisch et al., 2013; Walrand et al., 2021). Therefore, supporting the growth of beneficial bacteria in the gut microbiota by dietary fiber with prebiotic (a substrate selectively used by host microorganisms and provides health benefits) properties may be an important factor in brain injury recovery (Al-Ayadhi et al., 2021; Walrand et al., 2021).

The MIND diet includes important fibers (oligosaccharides, plant polyphenols, polyunsaturated fatty acid, conjugated linoleic acid, etc.) and fiber sources (whole grains, vegetables, beans, fruits, and nuts) that are prebiotic (Al-Ayadhi et al., 2021; Morris et al., 2015; Ramezani Ahmadi et al., 2020; Tillisch et al., 2013). Therefore, this diet model can support the proliferation of beneficial bacteria in the gut microbiota with the fibers showing prebiotic properties (Lockyer & Stanner, 2019; Nagpal et al., 2019). In this way, fibers help sustain the integrity of the gastrointestinal barrier by decreasing intestinal permeability (Al-Ayadhi et al., 2021). Furthermore, fibers support the release of neurotransmitters like brain-derived neurotrophic factor (BDNF) and gamma-aminobutyric acid (GABA), as well as the metabolites of short-chain fatty acids (SCFAs), which are produced by bacteria that consume prebiotics (Al-Ayadhi et al., 2021; Ramezani Ahmadi et al., 2020; Tillisch et al., 2013). These neurotransmitters and metabolites are involved in modulating inflammatory responses, promoting bidirectional communication among the microbiota, gut and brain called the microbiota-gut-brain axis (MGBA) thereby influencing the CNS while maintaining homeostasis in a healthy way (Poblete et al., 2023).

Since gut bacteria are involved in the metabolic processes of brain injury, maintaining MGBA homeostasis by consuming dietary fiber sources included in the MIND diet with prebiotic properties can be beneficial for improving possible negative neurological consequences induced by increased intestinal permeability.

2.3. Polyunsaturated Fatty Acids

The MIND diet includes essential PUFAs. Among these fatty acids omega-3 (ω-3) PUFAs like alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are some of the most studied and important for brain health (Nishi et al., 2023; Lăcătușu et al., 2019; Scrimgeour & Condlin, 2014). ALA, a plant-based ω-3 fatty acid, especially found high in nuts like walnuts supports neural processes such as axonal and dendritic growth, synaptogenesis, neurogenesis, and myelination, especially in terms of brain development from an early age (Chauhan & Chauhan, 2020; Nishi et al., 2023). It suppresses inflammation and oxidative stress by inhibiting nitric oxide (NO) production and proinflammatory cytokines such as IL-6, IL-1β, and TNF-α. ALA is the precursor for EPA and DHA (abundant in oily cold-water fish species) which are structural components of cell membranes, regulating membrane fluidity, flexibility, cell signalling, and mitochondrial function (Chauhan & Chauhan, 2020). DHA is also the main component of phospholipids, supporting neuronal plasma membranes (Arnoldussen & Kiliaan, 2014).

After brain damage cell membrane metabolism could be changed. Microglia has been considered the main cell regulator for the immune response of the CNS. It becomes more active than a passive state after brain damage and triggers an inflammatory cascade (Poblete et al., 2020). So proinflammatory cytokines are released (Martínez et al., 2023). In this case, BBB disruption occurs and exacerbates neuroinflammation leading to brain damage (Poblete et al., 2020; Poblete et al., 2023). Endogenous lipid mediators such as thromboxanes, prostaglandins, and leukotrienes produced from the hydrolysis of omega-6 (ω-6) rich membranes increase the infiltration of neutrophils along with disrupted BBB. These specialized pro-resolving lipid mediators (SPMs) can negatively regulate the inflammatory process thus leading to pain, fever, increased vascular permeability, and soft-tissue edema (Poblete et al., 2020). On the other hand, lipoxins which are another ω-6-derived SPMs can modulate granulocyte recruitment into injured tissue and attenuate neuroinflammation by promoting apoptosis of leukocytes (Poblete et al., 2020; Tiberi & Chiurchiù, 2021). Above all, SPMs derived from EPA and DHA ω-3 fatty acids like resolvins, protectins, and maresins take part in attenuating neuroinflammation by removing pathogens, decreasing leukocyte-infiltration, and promoting macrophage-mediated cellular debris phagocytosis. Since those SPMs having beneficial effects in alleviating neuroinflammation are mostly derived from ω-3 fatty acids, it is thought that ω-3 fatty acids protect nerve cells more than ω-6 fatty acids (Guo et al., 2016; Musto et al., 2015; Poblete et al., 2020; Scrimgeour & Condlin, 2014).

Specific to ω-3 fatty acids, there are studies conducted on American football players, in which the effects of different doses and formulas of ω-3 fatty acids supplementation on some biomarkers of brain damage and inflammation have been investigated (Heileson et al., 2021; Mullins et al. 2022; Oliver et al., 2016). Even one of these studies has found attenuation in biomarkers of brain damage (Heileson et al., 2021), others reported that ω-3 fatty acids did not mitigate the adverse effect of brain damage and inflammation (Mullins et al. 2022; Oliver et al., 2016). This indicates an inability to establish a direct consensus

that ω-3 fatty acids improve brain damage in American football players. PUFAs may support brain health in general, but more clinical research is required (Derbyshire, 2018; Poblete et al., 2020).

2.4. Monounsaturated Fatty Acids

The MIND diet recommends to prefer olive oil as the primary oil. Olive oil is rich in oleic acid (ω-9), which is one of the MUFAs (Lăcătușu et al., 2019; Morris et al., 2015). It has been indicated that MUFAs have neuroprotective features and oleic acid is the primary MUFA in the brain (Bazinet & Laye, 2014; Carrillo et al.,2012). Oleic acid is contained within neuronal membranes and high levels in myelin (Bazinet & Laye, 2014).

In a human study, the oleic acid levels were elevated in the cerebrospinal fluid 48 hours after the brain injury (Pilitsis et al., 2003). It has been considered that the increase in MUFA-containing phospholipids in the brain after brain damage may trigger the activation of neuroprotective mechanisms. On the other hand, a decrease in MUFA at later stages can contribute to the neurodegeneration following amyloid deposition (Ojo et al., 2019). A diet enriched with high oleic acid has been shown to exert neuroprotective effects by increasing amyloid clearance enzymes and diminishing amyloid plaques in mice (Amtul et al., 2011). Further, oleic acid has been associated with reduced oxidative stress, increased myelination and neurotropic support (Carrillo et al., 2012; Medina & Tabernero, 2002; Ojo et al., 2019).

According to studies and recommendations, the MIND diet model including balanced consumption of foods rich in both PUFAs (especially with a higher ω-3/ω-6 fatty acids ratio) and MUFAs (mainly oleic acid) could be advantageous for supporting brain health in American football players. Figure 1 summarizes the potential beneficial effects of the MIND diet components on brain health for American football players.

3. Conclusion

The MIND diet could have been considered to support brain health in American football players because it includes foods rich in bioactive components, fiber, PUFAs, and MUFAs. These MIND diet components could help to achieve the desired neuroprotective improvements against brain damage with their anti-inflammatory and antioxidant capabilities, besides regulating intestinal homeostasis, and modulating brain cell membrane, thereby restoring BBB disruption, neuroinflammation, and other neurological imbalances.

Although the MIND diet components may have been considered to improve the outcomes of brain damage depending on head impacts, integrating this type of nutrition model into regular practice does require discipline to comply with the recommendations on food consumption frequency and preference. Restriction on the consumption frequency of some foods may not be easy to adopt. Therefore, this diet model should be explained to athletes before being adopted. Since there is no literature on applying the MIND diet model for brain health in American football players, future studies would better focus on this topic by conducting randomized controlled clinical trials.

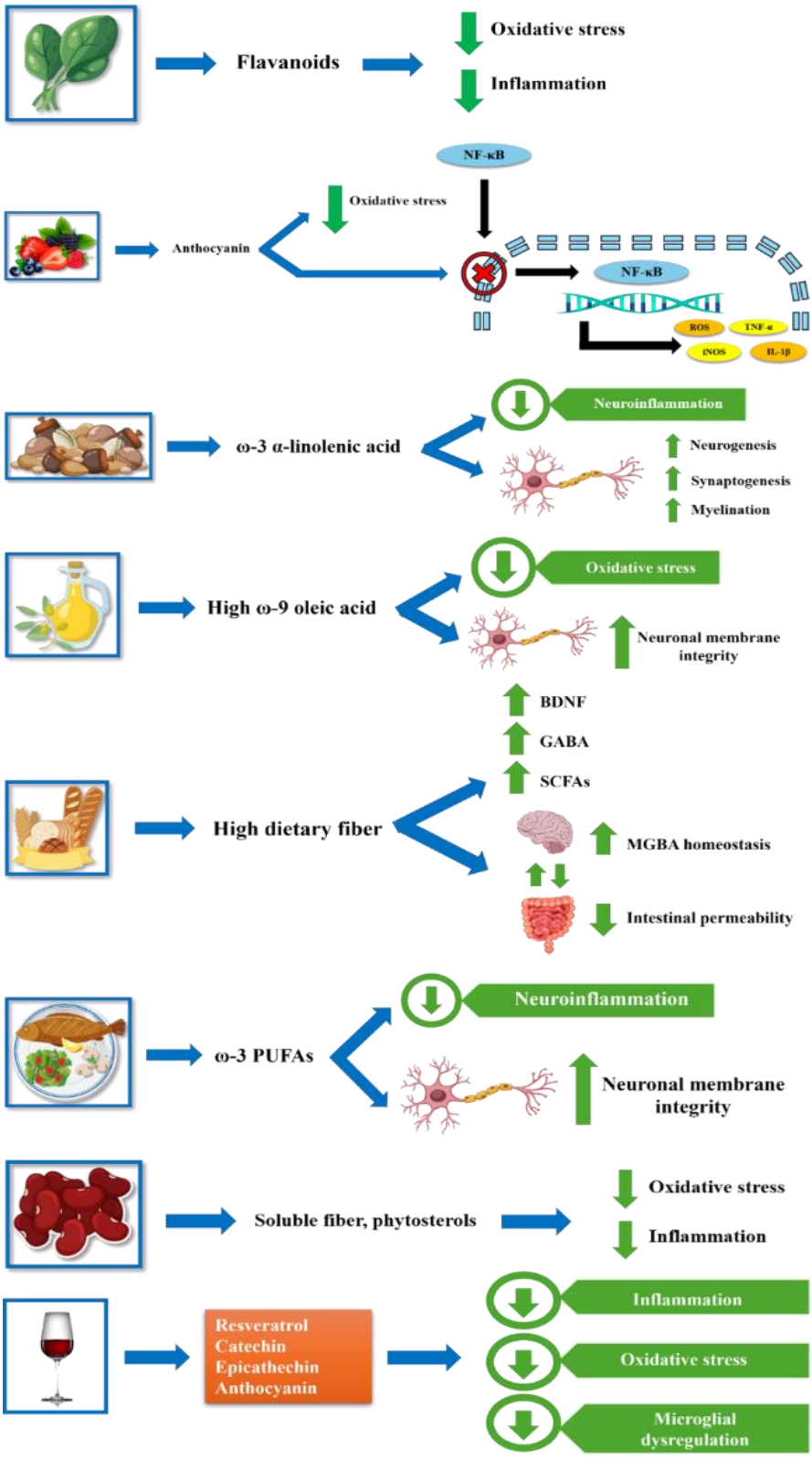

Figure 1. The Potential Effects of MIND Diet Components on Brain Health (Freepik was used for images) (Adapted from Ardekani et al., 2023)

Abbreviations: BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; IL-1β, interleukin 1 beta; iNOS, inducible nitric oxide synthase; MGBA, microbiota-gut-brain axis; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; TNF-α, tumor necrosis factor-alpha; ω, omega.

Ethical Statement

There is no need to obtain ethics committee permission for this study due to it is review article.

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Presentation Information

The findings of this study have not been presented at any conference or journal.

Conflicts of Interest

The authors declare no conflicts of interest regarding this study. Any institution or organization providing funding for this research did not have any role in the design, data collection, analysis, interpretation, or publication to influence or distort the findings.

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Review

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Mandibular Gingival Recessions: A Challenge of Achieving Complete Root Coverage in Periodontal Plastic Surgery?

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Abstract

Management of gingival recession has been one of the primary interests of periodontal research for many years. Periodontal plastic-aesthetic surgery has advanced due to the understanding of periodontal conditions, anatomical factors and integration of recession classification into pre-operative planning. As a result, complete root coverage is achieved frequently in most cases and has become the criterion for success. However; mandibular gingival recessions still proved to be a challenge for clinicians when widely accepted techniques that showed high predictability of root coverage were applied. To address this clinical condition on the mandible, innovations of accepted surgical procedures have been published. In the present review, we compiled and elucidated the developments made in the treatment protocols for mandibular gingival recessions.

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1. Introduction

Gingival recessions (GR) are defined as 'the apical shift of gingival margin caused by different conditions and/ or pathologies, associated with clinical attachment loss (Jepsen et al., 2018). This condition, when present, can impair patient aesthetics and comfort (i.e., hypersensitivity) (Nieri et al., 2013; Vignoletti et al., 2020), but may also increase the risk for root caries (Bignozzi et al., 2014; Cortellini & Bissada, 2018).

Factors such as aggressive toothbrushing (Baker & Spedding, 2002; Gorman, 1967; Kassab & Cohen, 2003), traumatic occlusion (Akerly, 1977), foreign body reactions (i.e., piercing, removable prosthetics) (Er et al., 2011), anatomical variances of gingiva and bone (e.g, lack of keratinized tissue (KT), thin soft/hard tissue phenotype, alveolar dehiscence) (Gorman, 1967; Kassab & Cohen, 2003; Wennström, 1996), aberrant frenulum (Kassab & Cohen, 2003; Wennström, 1996), and iatrogenic factors contribute to GR. While maintaining good periodontal health may negate the need for a minimum amount of KT (Jepsen et al., 2018), adequate keratinized gingiva (≥ 2 mm KT, ≥ 1 mm attached gingiva) promotes gingival health and insufficient KT with poor plaque control may lead to GR and inflammation (Kim & Neiva, 2015; Patel et al., 2011). In addition, untreated buccal gingival recessions often show an increase in recession depth (RD) (Chambrone & Tatakis, 2016).

The mandibula exhibits a higher prevalence of GR than the maxilla, with mandibular incisors most frequently affected, followed by maxillary molars and mandibular premolars (Mythri et al., 2015). Deep GR on mandibular incisors is commonly observed in patients with a history of orthodontic treatment, likely due to the direction of tooth movement and bucco-lingual gingival thickness (Renkema et al., 2013; Kim & Neiva, 2015).

The treatment of these conditions is well-documented but varies in predictability based on recession type and tooth (Cairo et al., 2011; Chambrone & Tatakis, 2015; Zucchelli et al., 2018) and success in mandibular sites is less predictable than in maxillary sites (Chambrone & Tatakis, 2015; Zucchelli et al., 2018), largely due to anatomical factors like the high insertion of the labial frenulum, thin marginal tissue, and limited vestibular depth, all of which make surgery on the mandibular incisors particularly challenging (Zucchelli et al., 2014). Additionally, caution is required around the mental nerve to prevent injury (Mazzotti et al., 2023).

Considering the data from the literature, the treatment of mandibular GR requires unique surgical viewpoints and techniques to consider. Furthermore, since mandibular GR has posed significant challenges, researchers have explored various methods to achieve root coverage with minimal post-operative morbidity or have modified existing techniques to improve outcomes. Therefore, this review aims to present and compile periodontal plastic surgical techniques used for the treatment of mandibular GR, with a focus on root coverage outcomes (RC).

2. Free Gingival Graft (FGG)

The use of pedicle grafts, particularly free gingival graft (FGG) (Bjorn, 1963; Edel, 1974; Haggerty, 1966; Nabers, 1966; Sullivan & Atkins, 1968), was

proposed in order to increase the width of KT and soft tissue volume as the understanding of genetic determinants of gingival tissues advanced in subsequent years (Karring et al., 1975; Karring et al., 1975; Karring et al., 1971). In the 1970s, the concept of RC began to replace the focus on increasing KT in mucogingival surgery (Figure 1). FGG became the first step in a two-stage surgery to create an attached gingiva before coronally positioning the flap for GR reduction (Bernimoulin et al., 1975; Harvey, 1970). Miller's GR Classification (Miller Jr, 1985) later highlighted both the limitations and effectiveness of FGG as a single-step procedure for RC.

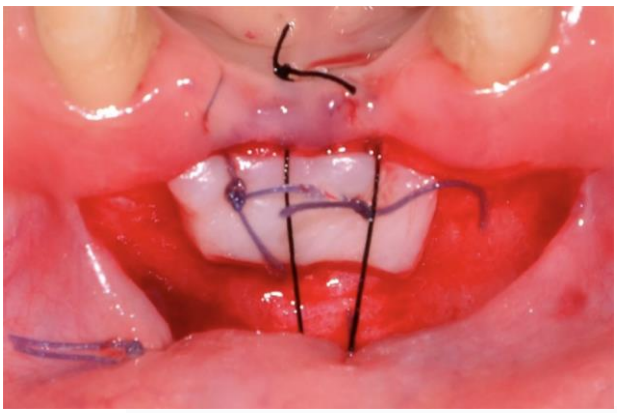

Figure 1. Free Gingival Graft for Keratinized Tissue Augmentation

2.1. FGG for RC Outcomes

Throughout the 1970s and 1980s, FGG remained the gold standard in mucogingival surgery (Prato & Gianfilippo, 2023). However; the majority of previous studies have not included the distinction between maxillary recessions from mandibular recessions (Jahnke et al., 1993; Liu & Solt, 1980; Matter, 1979; Miller Jr, 1985; Miller Jr, 1987; Paolantonio et al., 1997). The reasoning could be attributed to the high predictability of surgery and favourable prognosis where 100% RC is anticipated in Miller I and II cases regardless of the location (Camargo et al., 2001; Miller Jr, 1985) (Figure 2).

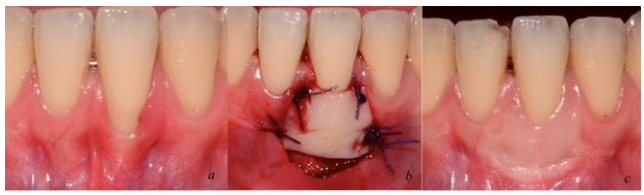

Figure 2. Free Gingival Graft for Root Coverage

A systematic review on mandibular Miller I/II/III and RT 1&2 recessions reported that FGG achieved a mean MRC of 8.5% and CRC of 14% (Agusto et al., 2022), with lower predictability likely due to anatomical limitations and the inclusion of varied recession types. Limited data exists on Miller IV recessions treated with FGG (Miller & Binkley, 1986), as reviews have largely focused on connective tissue grafts (CTG) for Miller III/IV cases (Bertl, Spineli, Mohandis, & Stavropoulos, 2021; Aitziber Fernández-Jiménez et al., 2021). Despite frequent aesthetic limitations (Camargo et al., 2001; McGuire, 1990; Miller Jr, 1987), innovations like modified FGG (modFGG) which translocates pedicle connective tissue beneath FGG have shown promising results for RC outcomes (Carcuac et al., 2023). Thus, according to the evidence presented in case series and randomized controlled clinical trials, FGG is still relevant for RC in anterior mandibular Miller I/II and RT I cases (Table 1).

3. Connective Tissue Graft (CTG)

The 1980s marked a revolutionary shift in periodontal plastic and aesthetic surgery. Langer and Langer pioneered the use of CTG underneath a split-thickness pedicle flap, partially covering the graft to improve RC and aesthetics (Langer & Langer, 1985). In the same year, Raetzke developed an '*envelope*' technique, using intrasulcular partial-thickness

incisions to create a foundation for tunnelling methods, aiming for minimal morbidity and enhanced aesthetics (Raetzke, 1985). Nelson later refined CTG with bilaminar grafting', using sliding and double papilla flaps to improve vascularization and prevent necrosis, enhancing surgical outcomes (Nelson, 1987). In 1994; Bruno further modified Langer & Langer technique (Langer & Langer, 1985) by using only horizontal incisions at the CEJ and internal dissection of the flap; omitting vertical incisions entirely; to achieve RC and aesthetics (Bruno, 1994). Following this paradigm shift in literature; the still widely applied version of ''bilaminar technique'' has been presented in literature (Zucchelli et al., 2003).

Table 1. Root Coverage Outcomes from Studies Involving Mandibular Gingival Recession- Free Gingival Graft

Study	Year	Diagnosis	Intervention	MRC	CRC	Follow-Up
Kuru & Yıldırım (Kuru & Yıldırım, 2013)	2013	Miller I & II	• FGG • Gingival Unit + FGG	67% 91.6%	0% 50%	8 months
Goyal (Goyal, Gupta, Gupta, & Chawla, 2019)	2019	Miller I & II	• FGG	82.22%	NR	9 months
Yılmaz (Yilmaz, Comerdov, Kutuk, Nart, & Keceli, 2022)	2022	RT 1 & RT 2	• FGG	63.5%	20%	12 months
Parlak (Parlak, Yilmaz, Durmaz, Toz, & Keceli, 2023)	2023	RT 1 & RT 2	• FGG	63.95%	26.3%	6 months
Carcuac (Carcuac, Trullenque-Eriksson, & Derks, 2023)	2023	RT 1	• FGG • modFGG	60.7% 91.8%	0% 88%	12 months

3.1. Coronally Advanced Flap (CAF)

Allen and Miller (1989) introduced a simplified approach to correct GR by coronally advancing the flap with two vertical incisions on the mesial and distal papilla, without any soft tissue graft (Allen & Miller, 1989). This technique later became foundational, modified for routine periodontal aesthetic surgery to achieve reliable RC (Zucchelli et al, 2003; De Sanctis & Zucchelli, 2007). Zucchelli et al. (2000) further refined this by eliminating vertical incisions to treat multiple GR sites more effectively (Zucchelli & De Sanctis, 2000).

3.2. CTG + CAF

In 1992; complete coverage of CTG with CAF as a predictable method for RC has been proposed by Harris (Harris, 1992). Building on Edel's graft acquisition (1974) (Figure 3) and techniques by Langer & Langer (1985) and Nelson (1987), Harris declared that '*'predictable root coverage is a reality''* and an ''*obtainable goal''* (Edel, 1974; Langer & Langer, 1985; Nelson, 1987; Harris, 1992). Later studies confirmed this approach's effectiveness (Jahnke et al., 1993; Wennström, 1996) and further refinements; including split-full-split thickness flaps and CEJ-based incisions; improved predictability and

aesthetics (de Sanctis & Zucchelli, 2007; Zucchelli et al., 2003).

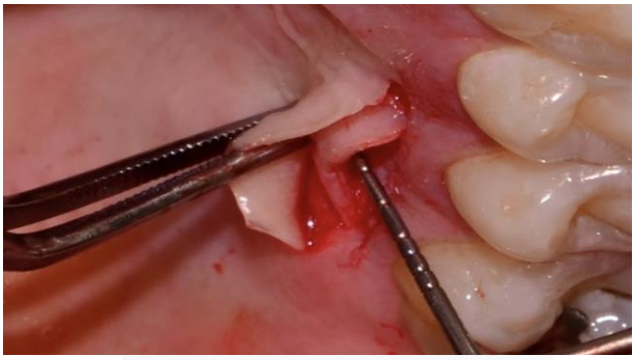

Figure 3. Connective Tissue Graft Acquisition

CTG has since become central to achieving CRC and aesthetic outcomes over CAF alone (Cortellini et al., 2009; Zucchelli et al., 2003). Zuhr et al. (2014) theorized '*that the presence of CTG could stabilize the CAF and eventually serve as an '**anchor**' for the covering flap during initial wound healing*' (Zuhr et al., 2014). CTG + CAF is now considered the gold-standard for reliable CRC and MRC outcomes (Chambrone et al., 2019; Chambrone & Tatakis, 2015) (Figure 4).

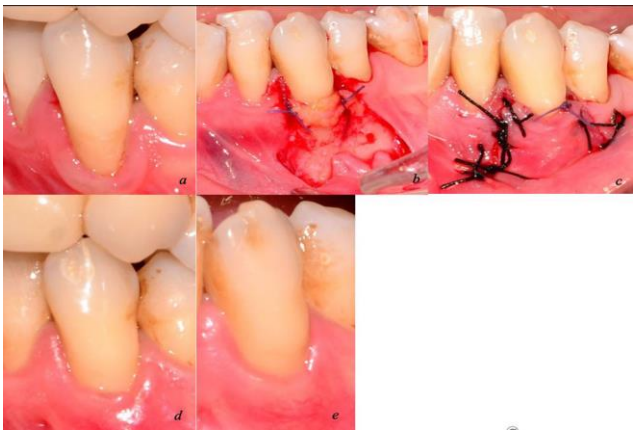

Figure 4. Connective Tissue Graft + Coronally Advanced Flap

3.3. CAF and CTG + CAF on RC Outcomes

As the CAF and CTG + CAF became standard in periodontal plastic-aesthetic surgery (Chambrone et al., 2019), numerous studies documented their predictability and success in RC outcomes and the aim of the research has focused on achieving CRC (Cairo et al., 2010; Cairo et al., 2009). Recent studies further support CRC as the most anticipated outcome by reporting >80% MRC and at least 66% of patients obtaining complete recession reduction (Bertl et al., 2021).

Nevertheless; the treatment of GR involving mandibular incisors has been a challenge for it has been shown to have varying RC outcomes ranging from 53.8% to 75% (Zucchelli et al., 2018) and the literature has presented modifications of existing procedures in order to address this (Carcuac et al., 2023; Fernández-Jiménez et al., 2024; Sculean & Allen, 2018; Stefanini et al., 2021; Zucchelli et al., 2014).

3.4. V-CAF (Vertically CAF)

Zucchelli et al. presented the removal of labial submucosal tissue (LST) added to the trapezoidal-type of CAF (de Sanctis & Zucchelli, 2007) which resulted in the creation of a vertical dimension for CAF (Zucchelli et al., 2014). By eliminating LST, they intended to prolong the muscle reattachment that would cause early shrinkage of CAF and achieve a tension-free closure (Zucchelli et al., 2014). Recent clinical data have promising results on V-CAF for increasing vestibular depth, tissue thickness and aesthetics which indicates that it is a highly preferable alternative to FGG. However, there is no consensus yet for which technique is more predictable in obtaining RC and CRC at mandibular anterior teeth (Parlak et al., 2023; Stefanini et al., 2021; Zucchelli et al., 2014). Table 2 summarizes the results of clinical trials, case series, and randomized controlled clinical

studies that assessed the effectiveness of CAF+ CTG in treating RC for mandibular teeth.

Table 2. Root Coverage Outcomes from Studies Involving Mandibular Gingival Recession- Coronally Advanced Flap Techniques+ Connective Tissue Graft

Study	Year	Diagosis	Intervention	MRC	CRC	Follw-up
Harris (Harris et al., 2005)	2005	Miller I & II	CAF+CTG	80.2%	NR	3 months
De Sanctis (de Sanctis et al., 2011)	2011	Miller I & II (Posterior)	CAF+CTG	91.2%	%50	12 months
Nart (Nart et al., 2012)	2012	Miller II & III	CAF+CTG	90.22%	57.14%	11.7 months
Zucchelli (Zucchelli et al., 2014)	2014	Miller I & II (> 3 mm depth)	CAF+CTG V-CAF+CTG	NR	48% 88%	12 months
Mercado (Mercado et al., 2020)	2020	Miller III & IV	CAF+CTG CAF+CTG+EMD	57.2% 68.36%	0% 10%	36 months
Stefanini (Stefanini et al., 2021)	2021	RT 1	V-CAF	98.3%	90%	12 months
Parlak (Parlak et al., 2023)	2023	RT 1 & RT 2	V-CAF	70.34%	47.4%	12 months

4. Tunnel Technique (TUN)

Raetzke's '*envelope*' technique focused on treating isolated recession defects with minimal post-operative morbidity (Raetzke, 1985). However, in 1994, Allen improved upon the 'envelope technique' with a partial thickness internal dissection in order to address multiple adjacent gingival recessions while achieving minimal surgical trauma, incorporating vascular supply of CTG from intact lateral and papillary gingiva and improving aesthetics by maintaining papillary integrity (Allen, 1994). Over the following years, many modifications have been made to the TUN including different suturing techniques, flap designs and preservation of intermediate papillae (Tözüm & Dini, 2003; Zabalegui et al., 1999). Coronally advancement of TUN over CTG came into consideration by Azzi et al. (Azzi & Etienne, 1998; Azzi et al., 2002) and it has been applied since with different methods (Mahn, 2001; Zadeh, 2011) and microsurgical intentions (Zuhr et al., 2007) to achieve more predictable results with improved aesthetics (Aroca et al., 2010; Blanes & Allen, 1999; Tavelli et al., 2018; Zuhr et al., 2007) (Figure 5). Although the literature has established that TUN is immensely effective in treating GR (Mayta-Tovalino et al., 2023), Tavelli et al. (2018) reported that CAF has been shown to be more predictable compared to TUN in achieving CRC (Tavelli et al., 2018). Contrarily, recent studies have stated that both techniques are significantly similar in achieving RC and CRC (Chang et al., 2024; González-Febles et al., 2023; Mayta-Tovalino et al., 2023) and their existence represents versatility in periodontal plastic aesthetic surgery (Chang et al., 2024).

Figure 5. Tunnel Technique + Coronally Advancement

4.1. Laterally Closed Tunnel (LCT)

Especially in the mandibular anterior area, the risk of flap perforation and flap necrosis is stated to be an issue to overcome and as an alternative to conventional methods; a '*Laterally Closed Tunnel*' was developed as a modification of TUN by means of suturing tunnel margins (Sculean & Allen, 2018). Following this idea, further clinical trials were conducted focusing on LCT with promising results (Lavu et al., 2022; Quispe-López et al., 2022). In Table 3, the RC outcomes in case series, clinical trials, and randomized controlled clinical trials involving the use of the tunnel technique and its modifications in the treatment of mandibular GR were assessed.

Table 3. Root Coverage Outcomes from Studies Involving Mandibular Gingival Recession- Tunnel Techniques + Connective Tissue Graft

Study	Year	Diagnosis	Intervention	MRC	CRC	Follow-Up
Harris (Harris et al., 2005)	2005	Miller I & II	TUN-LAT + CTG	90.25%	NR	3 months
Sculean (Sculean et al., 2014)	2014	Miller I & II	modTUN + CTG	96.25%	75%	12 months
Thalmair (Thalmair et al., 2016)	2016	Miller I & II	modTUN + CTG	93.87%	74.6%	6 months
Sculean and Allen (Sculean & Allen, 2018)	2018	Miller I & II & III (≥ 4 mm depth)	LCT + CTG	96.11%	70.83%	12 months
Guldener (Guldener et al., 2020)	2020	RT 1 (≥ 3 mm depth)	LCT or modTUN + CTG + HA	96.09%	50%	6 months
Skierska (Skierska et al., 2022)	2022	RT 1 & RT 2	modTUN + CTG	93.6%	87.29%	24 months
Quispe-Lopez (Quispe-López et al., 2022)	2022	Miller II & III	LCT + CTG	96.4%	85.7%	16.7 months
Yılmaz (Yilmaz et al., 2022)	2022	RT 1 & RT 2	modTUN+ CTG	85.82%	35%	12 months

5. The Importance of Classification of Gingival Recessions, Tooth Location, and Anatomical Considerations on RC Outcomes

The development of GR research led to the isolation of Miller III cases before there was a full understanding of the predictability of RC in relation to tooth position and location. Researchers have since reported favourable outcomes for MRC, with CRC being a possibility in some cases (Aroca et al., 2010; Esteibar et al., 2011). Thus, further investigation has been made to present the efficacy of GR treatments on Miller III/RT 2 cases for CRC outcomes. Jimenez et al. (2021) have stated that modern literature has presented a CRC rate of 51.11% at 6-month follow-up which later decreased to 32.87 % at 12 months and 19.65% at follow-ups greater than 12 months, concluding that achieving CRC on Miller III/RT 2 class recessions is still not predictable (A. Fernández-

Jiménez et al., 2021). For Miller IV cases, it has been stated that improvement of clinical parameters can be expected but the amount of RC cannot be anticipated (Chambrone & Tatakis, 2015) and literature has limited data on long-term RC stability for Miller III and Miller IV GRs (Bertl et al., 2021).

Considering the evidence-based information in the literature, periodontal plastic and aesthetic surgery research has an abundance of data involving maxillary GRs but not as much for exploring the treatment of mandibular GRs (Chambrone & Tatakis, 2015; Tonetti & Jepsen, 2014; Zucchelli et al., 2018). Previous research indicated that treating maxillary GR has resulted in greater recession depth reduction (Chambrone & Chambrone, 2006). As anatomical differences between the maxilla and mandible became evident—such as narrow papilla dimensions in the mandible, the presence of lip muscles, and reduced vestibular depth (de Sanctis & Zucchelli, 2007)—the challenges for clinicians became clearer. This understanding would later drive the literature towards developing and refining existing techniques to improve the predictability of RC in the mandibular jaw (Fernández-Jiménez et al., 2024; Sculean et al., 2016; Stimmelmayr et al., 2011; Zucchelli et al., 2014). Interestingly, recent studies have not revealed any significant difference between mandibular and maxillary GRs treated with CAF (Zucchelli et al., 2018) or Tunnel (Skierska et al., 2022).

Furthermore, Zucchelli et al. (2018) reported higher MRC and CRC in anterior teeth, while postulating that the amount of KT, gingival thickness and initial clinical attachment level (CAL) could be a determining factor for anticipating RC (Zucchelli et al., 2018).

6. Conclusion

Obtaining CRC and MRC have varying results despite the technique utilized for the treatment of mandibular GRs. Furthermore, the literature has not reached a consensus on the ideal choice of treatment and more RCTs are still needed. Research has shown that the classification of GRs is a reliable indicator of anticipating RC, even though great care should be given to anatomical circumstances for each individual recession and the ideal technique could be decided based on the amount of KT, gingival thickness and initial CAL as mandibular incisors are more frequently affected by GR. To overcome the challenge of mandibular recessions, clinicians should be aware of recession depth, cervically inserted frenulum, orthodontic treatment involvement and habit-induced oral trauma.

Ethical Statement

There is no need to obtain ethics committee permission for this study due to being a review. However, the study was conducted in accordance with ethical principles.

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Presentation Information

This study has not been presented at any conference or journal.

Conflicts of Interest

The authors declare no conflicts of interest regarding this study. Any institution or organization providing funding for this research did not have any role in the design, data collection, analysis, interpretation, or publication to influence or distort the findings.

Author Contributions

The contributions of the authors are as follows: Ahmet Çağlar Kalkan participated in data collection, analysis and prepared the draft of the paper; Burcu Özdemir conducted multiple revisions of the manuscript; Sıla Çağrı İŞLER conducted the final revision of the manuscript.

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Evaluation of the Phytochemical Contents and Biological Activities of 'Dandelion' (*Taraxacum officinale* F.H.Wigg.): A Review

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Abstract

Taraxacum officinale F.H.Wigg. commonly known as the dandelion, is a plant that is widely distributed across the globe and can easily thrive in gardens, lawns, and along roadways. This paper aims to compile studies on this readily available plant's pharmacological properties and phytochemical composition. Dandelion is recognized worldwide for its gastrointestinal benefits, supporting digestion and liver functions, and it is known to possess numerous pharmacological activities. These activities are attributed to its rich phytochemical profile. The primary effects of plants with varied components are typically linked to compounds such as taraxol, taraxerol, and sesquiterpene lactones.

Furthermore, dandelion roots are rich in inulin, making the plant versatile for various applications in daily life. The scientific literature shows no reports of dandelion toxicity or serious adverse effects in humans. The potential value of dandelion increases due to its ease of cultivation, diverse pharmacological activities stemming from its rich phytochemical content, and low toxicity profile.

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1. Introduction

Medicinal plants have been used since the dawn of humanity to prevent and treat diseases. In the past, they were commonly utilized for basic needs such as nutrition and health. However, they are often chosen under the mistaken belief that "natural is harmless." In reality, plants contain many primary and secondary metabolites, which can have unintended effects. These effects and interactions between plant metabolites and drugs or nutrients may lead to adverse outcomes. To safeguard public health, it is essential to have reliable sources of information about plants and individuals who are well-informed. Therefore, it is crucial to access the right plant for the intended benefit and use it responsibly. This study aims to provide a comprehensive summary of the dandelion, including general information, its chemical structure, pharmacological effects, toxicity, and essential details for its proper use.

2. General Information

Dandelion (*Taraxacum officinale* F.H. Wigg), a member of the Asteraceae family, is widespread in every part of the world. Still, it grows most commonly in Europe, North Africa, and West Asia. The perennial herbaceous plant does not rise very high from the ground. Dandelion is included in many Monographs and Pharmacopoeias due to its medicinal effects (Kayıran et al., 2020). The European Scientific Cooperative on Phytotherapy (ESCOP) stated that dandelion roots can be used to treat dyspepsia and restore hepatic and biliary functions. According to the German Commission E, the dandelion roots can also be used for biliary abnormalities, appetite loss, dyspepsia, and stimulation of diuresis (Cheema & Singh, 2021).

2.1. Botanical information

It has long and toothed rosette leaves, single yellow flowers rising from the middle, and a thick taproot. Its fruit consists of numerous seeds with parachute-like feather-like tips. The seeds of the spherical fruits are dispersed by the wind and spread far away. When the leaves and stem of the plant are cut, the bitter milk-like ‘latex’ is released (Başer, 2016).

3. Traditioanal Usage of *Taraxacum officinale*

Dandelion, an edible medicinal plant, and vegetable, has long been used in traditional medicine and folk remedies to treat various diseases in many countries (Fan et al., 2023). In traditional use, findings have been recorded that dandelion was used in the 10^{th} and 11^{th} centuries to treat disorders such as indigestion, heartburn, hepatitis, anorexia, gout, and diarrhea. In traditional Chinese medicine, dandelion is recorded to be used as an immune booster against hepatitis, upper respiratory tract infections, bronchitis, and pneumonia and as a topical compress to treat mastitis. In addition, dandelion roots and leaves are used to treat stomach problems, appendicitis, anemia, jaundice, high fever, eye problems, gastrointestinal problems, eczema, uterine and breast cancer, and to improve the function of the digestive system. Native Americans use dandelion as a diuretic in the treatment of kidney diseases and stomach disorders. In Indian and Russian folk medicine, dandelion is known as a liver tonic. In Iran, it is used for liver and kidney diseases (Jalili et al., 2020). In traditional Indian medicine, it is used to

treat chronic ulcers, tuberculosis, bloating, colic, kidney disorders, gout, jaundice, and gallstone disorders. In Europe, it is used to treat high fever, urinary tract infections, eye problems, diabetes, and diarrhea. It has also been used in traditional medicine to treat eczema and various skin diseases. It is known that dandelion has been an essential component of traditional medicine for at least a thousand years (Kayıran et al., 2020). The plant is used as a mild laxative, diuretic, bile stimulating, and antidiabetic drug in Türkiye (Keçeci, 2011).

4. Phytochemical Contents of *Taraxacum officinale*

Dandelion has a highly diverse phytochemical structure, encompassing both primary and secondary metabolites. One of the most important secondary metabolic groups in the plant is sesquiterpenoids, which impart the plant's characteristic bitter taste. The plant is rich in sesquiterpenoids and lactones, particularly germacrene, eudesmane, and guaiane-type sesquiterpene lactones. Its flowers, leaves, and roots contain significant amounts of phenolic acids, including chlorogenic acid, hydroxycinnamic acid, caffeoylquinic acid, cichoric acid and its isomer, caffeic acid, *p*-coumaric acid, ferulic acid, and quercetin. Dandelion also contains flavonoids such as quercetin, rutin, luteolin, and triterpenoids like taraxasterol and pseudotaraxasterol. It is a rich source of phytosterols, including *β*-sitosterol, stigmasterol, and campesterol, and has been reported to contain various pigments and volatile oils, such as chlorophyll and chrysophanol.

The roots of the dandelion are high in carbohydrates, including fructose, glucose, and sucrose, and contain inulin in amounts ranging from 2% to 40%. Its roots are consumed as bitter dandelion coffee in many countries. The leaves are a rich source of potassium, containing up to 5%, making them a common ingredient in salads and dishes. Dandelion is also an excellent source of vitamins (A, C, E, K, and B), minerals (calcium, sodium, magnesium, iron, copper, silicon, zinc, and manganese), fiber, and protein (Fan et al., 2023; Kayıran et al., 2020; Olas et al., 2022; Yan et al., 2024).

5. Safety of the Taraxacum officinale

Dandelion is highly regarded for its medicinal properties and is considered entirely non-toxic. Additionally, this plant is frequently consumed as food and is classified as safe for general use. The US Food and Drug Administration has listed dandelion as a safe product, even for individuals with rare allergies. According to the PDR monograph, the plant poses no health hazard when used appropriately (Gruenwald et al., 2000; Olas, 2022).

Studies on its biological effects have demonstrated a range of beneficial activities, including anti-inflammatory, antibacterial, antioxidant, hypolipidemic, antihyperglycemic, anticancer, diuretic, choleretic, antiplatelet, prebiotic, hepatoprotective, and gastroprotective effects. In vitro, animal, and clinical studies supporting these activities are reviewed here. The potential value of the dandelion plant is growing, as it can be easily cultivated, offers numerous benefits due to its rich phytochemical content, is not known to be toxic, and is classified as "GRAS" (generally recognized as safe) in the USA (Başer, 2016).

6. Biological Activity Studies

Results from many studies have shown that dandelion has numerous biological potentials, such as anti-inflammatory, antibacterial, antioxidant, hypolipidemic, antihyperglycemic, anticancer, diuretic, kidney-protective, choleretic, antiplatelet, hepatoprotective and gastroprotective, and also exerts a positive effect on gastric motility and *Bifidobacteria*.

6.1. Anti-inflammatory Activity

Kim et al. (2000) investigated changes in tumor necrosis factor-alpha (TNF-α) levels in astrocytes stimulated by substance P and lipopolysaccharide (LPS) in rats. When *Taraxacum officinale* (TO) (100 and 1000 μg/mL) was administered to astrocytes stimulated with LPS and substance P, TNF-α production was significantly reduced, and interleukin-1 (IL-1) production was also significantly decreased. After the study, it was reported that TO could prevent TNF-α production by inhibiting IL-1 production and demonstrated anti-inflammatory activity.

6.2. Anti-Bacterial Activity

In a study by Narkey et al. (2022), the antibacterial activity of extracts obtained through 70% ethanolic and methanolic extractions of fresh *Taraxacum officinale* leaves collected from Ghana was investigated. The antimicrobial activity of the *T. officinale* leaf extract against *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae* was evaluated using the agar well diffusion method. The results showed that *Staphylococcus aureus* was resistant to the ethanolic extract of *T. officinale* leaves. However, the ethanolic extract was effective against *E. coli* and *K. pneumoniae*. In contrast, the methanolic extract of *T. officinale* was found to be effective against all three bacteria. The study concluded that the methanolic extract of *T. officinale* leaves exhibited *in vitro* antibacterial activity against *S. aureus, K. pneumoniae*, and *E. coli* (Narkey et al., 2022).

6.3. Antioxidant Activit

Choi et al. (2010) investigated the hypolipidemic and antioxidant activities of dandelion root and leaf in rabbits fed a high-cholesterol diet. Twenty-eight male rabbits were divided into four groups: a normal diet group, a cholesterol diet group, a high-cholesterol diet group supplemented with dandelion root, and a high-cholesterol diet group supplemented with dandelion leaf. Plasma antioxidant enzymes and lipid profiles were assessed. Plasma AST concentrations showed a slight decrease in the dandelion leaf-fed group compared to the control group, while ALT activity was significantly reduced in the dandelion root-fed group. HDL cholesterol levels were significantly increased in the dandelion leaf-fed group, whereas triglyceride and LDL cholesterol levels were significantly decreased. The triglyceride levels in the dandelion root group were significantly lower than those in the control group. GSH activities were significantly higher in both the dandelion-fed groups compared to the control group. Additionally, representative aorta sections stained with hematoxylin-eosin were examined for all four groups. While the aorta sections of the control group rabbits were healthy, those of the high-cholesterol-fed groups showed plaque formation with lipid accumulation, a hallmark of atherosclerosis. Atherosclerosis-related problems were significantly reduced in both

dandelion-fed groups. Overall, the results indicated that antioxidant enzyme activity and lipid profiles improved with dandelion treatment. Therefore, it can be concluded that dandelion has hypolipidemic and antioxidant effects and is protective against the development of atherosclerosis.

6.4. Antihyperglycemic Activity

The effect of ethanol extract from *Taraxacum officinale* collected in Pakistan on insulin secretion was investigated. Air-dried and ground plant material (30 g) was extracted using 80-90% ethanol. The resulting extracts, prepared at concentrations ranging from 1 to 40 μg/mL, were tested for their effects on insulin secretion from INS-1 cells in the presence of glucose. Glibenclamide was used as a control. The results showed promising insulin secretagogue activity in *Taraxacum officinale* at a concentration of 40 μg/mL (Hussain et al., 2004).

Dandelion has also been shown to enhance glucose uptake in the body by stimulating insulin secretion in the pancreas. Taraxasterol (TS) contributes to the anti-hyperglycemic effect by inhibiting α-glucosidase and α-amylase, thus preventing the digestion of carbohydrates (Wirngo et al., 2016).

6.5. Hepatoprotective Activity

Hamza et al. (2020) evaluated the effects of dandelion on liver fibrosis. Liver fibrosis was induced in rats by administering 20% CCl_4 for 8 weeks. It was administered orally to adult male albino rats twice a week. Twenty-four rats were randomly divided into four groups (six rats each). Damaged liver histology was significantly improved by hematoxylin-eosin staining and histopathological scoring methods. Masson staining and hydroxyproline content method also showed that collagen accumulation in the region decreased. mRNA and protein levels of α-smooth muscle actin and collagen 1 and 3 decreased after dandelion treatment compared to the CCl_4 group. In addition, dandelion decreased inflammatory markers such as interleukin-IL-1β, tumor necrosis factor-α, cyclooxygenase-2, and nuclear factor kappa-B. In addition, oxidative stress also decreased myeloperoxidase activity, which is an indicator. The antifibrotic effects of dandelion can be attributed to its ability to scavenge free radicals and reduce the inflammatory process in cells.

6.6. Gastroprotective Activity

Zanatta et al. (2021) investigated the gastroprotective effects of *Taraxacum officinale* aqueous extract (AETo) in Wistar female rats. Forty rats were randomly divided into five groups, with 8 rats in each group. The dandelion plants were collected from Brazil in October 2019. The study examined the effect of the aqueous extract of dandelion on inflammatory and oxidative stress markers in damaged gastric tissue. Significant damage was observed in the gastric tissue of rats with ethanol-induced ulcers. Ethanol and piroxicam-induced gastric ulceration were treated orally with AETo at concentrations of 3, 30, and 300 mg/kg. The results showed that rats receiving 30 or 300 mg/kg AETo exhibited a significant reduction in the size of the ulcerated area, by 62.1% and 58.7%, respectively, compared to the saline-treated group. In the piroxicam-induced ulcer model, rats showed significant gastric tissue damage, but AETo at 30 and 300 mg/kg resulted in 75.4% and 88.8% reductions in

lesion areas, respectively, compared to the saline-treated group. The gastroprotective effect of AETo is attributed to its ability to reduce oxidative stress and inflammation, as well as to increase mucus content.

6.7. Diuretic Activity

A study investigating the diuretic activity of a hydroethanolic leaf extract of *T. officinale* examined its effects on urinary frequency and volume. Data on urine output and water intake were recorded for two days prior to the application of dandelion extract. Observations were made over a 24-hour period following the administration of the extract (8 mL, three times per day). In the entire study population (n = 17), a significant increase in urination frequency was observed during the 5 hours after the first dose. A similar significant increase in excretion was noted in the 5 hours following the second dose. However, no significant change was observed after the third dose. The study concluded that *T. officinale* increased both the frequency and volume of fluid excretion in healthy humans (Kayıran et al., 2020).

6.8. Prebiotic Activity

The roots of *T. officinale* were collected in Prague in 2003, dried, and ground 30 g of the root was infused in 100 ml of boiling water. After filtering the infusion, it was added to the broth medium at a concentration of 10%. *Bifidobacteria* grown in the Wilkins-Chalgren medium were added to the dandelion root extract medium. All cultures were incubated at 37 °C under anaerobic conditions for 48 h, and the results were recorded. Enzymatic and phenol-sulfuric methods determined the utilization of polysaccharides and glycosides. Dandelion root infusion stimulated the in vitro growth of 14 bifidobacteria (*B. adolescentis* 1, *B. adolescentis* 2, *B. animalis, B. bifidum* 1, *B. bifidum* 2, *B. breve, B. catenulatum, B. infantis, B. longum* 1, *B. longum* 2, *B. longum* 3, *B. longum* 4, *B. longum* 5, *B. pseudolongum)* strains (Trojanova et al. 2004).

6.9. Choleretic Activity

Bile-reducing effect; increases bile volume by increasing the rate of bile excretion from liver cells. This bile passes into the small intestine during digestion. It was recorded that bile secretion increased by 40% when an alcoholic extract obtained from the whole *Taraxacum officinale* plant was administered intraduodenally to rats (Keçeci, 2011).

7. Conclusion

Dandelion has many pharmacological activities that make it a valuable plant due to its low cost, high availability, and no severe toxicity reports. All studies conducted on the plant have shown great potential for use in many diseases due to the available published data on the plant. Studies conducted have generally focused on in vitro and animal experiments. More clinical studies are needed on the absorption, distribution, metabolism, elimination, bioavailability, and safety of the plant for drug and pharmaceutical studies. Studies have generally progressed on certain plant parts such as leaves and roots. In addition, the activities, and mechanisms of action of the effective active ingredients of the plant should be studied further. By combining traditional medicinal plants such as dandelion with today's pharmaceutical sector, more advanced treatment opportunities can be offered to people.

Ethical Statement

There is no need to obtain ethics committee permission for this study for review article reasons. However, the study was conducted in accordance with ethical principles.

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Presentation Information

The findings of this study have not been presented at any conference or journal.

Conflicts of Interest

The authors declare no conflicts of interest regarding this study.

Author Contributions

The contributions of the authors are as follows: R.Ş. wrote the manuscript and H.N.G. made the final revision of the article.

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