

# Vitamin B12: prevention of human beings from lethal diseases and its food application

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## Abstract

Vitamin B12, a water-soluble essential micronutrient, plays a pivotal role in numerous physiological processes in the human body. This review meticulously examines the structural complexity and the diverse mechanisms through which vitamin B12 exerts its preventive effects against a spectrum of health conditions, including pernicious anaemia, neurological disorders, obesity, diabetes, dyslipidaemia and complications in foetal development. The selection of articles for this review was conducted through a systematic search across multiple scientific databases, including PubMed, Scopus and Web of Science. Criteria for inclusion encompassed relevance to the biochemical impact of vitamin B12 on health, peer-reviewed status and publication within the last decade. Exclusion criteria were non-English articles and studies lacking empirical evidence. This stringent selection process ensured a comprehensive analysis of vitamin B12's multifaceted impact on health, covering its structure, bioavailable forms and mechanisms of action. Clinical studies highlighting its therapeutic potential, applications in food fortification and other utilizations are also discussed, underscoring the nutrient's versatility. This synthesis aims to provide a clear understanding of the integral role of vitamin B12 in maintaining human health and its potential in clinical and nutritional applications.

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**Keywords:** clinical studies; deficiencies; food applications; mechanism; structure; vitamin B12

## INTRODUCTION

Cobalamin, often known as vitamin B12, is a water-soluble vitamin essential for many physiological functions. It is naturally present in dairy products, ready-to-eat breakfast cereals, beef, chicken and fish.<sup>1</sup> It is necessary for the synthesis of DNA, the production of red blood cells, and the normal methylation and mitochondrial metabolism of the neurological system. Sustaining hemopoiesis and neurologic health requires vitamin B12.<sup>2</sup> A diet high in plant-based foods and low in animal products can boost health advantages, but a diet low in animal products causes B12 insufficiency.<sup>3</sup> Gastric acid within the stomach lumen initiates the cleavage of vitamin B12 from dietary protein complexes. Subsequently, the liberated cobalamin (vitamin B12) transiently binds to salivary R-proteins. This cobalamin-R-protein complex is degraded by pancreatic proteases in the duodenum, facilitating the release of cobalamin, which then binds with intrinsic factor (IF), a glycoprotein secreted by gastric parietal cells. The cobalamin-IF complex traverses to the distal ileum, where it binds to specific ileal receptors, allowing for endocytosis and intracellular absorption of cobalamin.<sup>4</sup> The liver releases vitamin B12 into the blood when it is needed. A variety of health issues, including anaemia, neuropathy, cognitive decline and psychiatric illnesses, can be brought on by deficiency.<sup>5</sup> The risk of experiencing a vitamin B12

deficiency increases in vegetarians, expectant mothers, people with malabsorption diseases such as pernicious anaemia and people with celiac illnesses. Vitamin B12 plays a significant role in

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homocysteine and methionine metabolism. Converting homocysteine to methionine, which also requires folate and vitamin B6, requires vitamin B12.<sup>6</sup> Homocysteine levels can increase without sufficient vitamin B12 levels, which may result in significant health issues.<sup>7</sup> Research has also investigated the benefits of vitamin B12 supplementation for many of the health conditions or deficiencies mentioned above. The best dosage and duration are still up for debate. Here, we provide a concise overview of the role of vitamin B12 in the human body, including its composition, structure and mechanism.

## STRUCTURE AND FORMS OF VITAMIN B12

Vitamin B12, known for its complex non-polymeric structure, features a corrin ring with a central cobalt ion, as depicted in Fig. 1. This molecule has a molecular weight of 1335 Da and typically exists in the cyanocobalamin form.<sup>8</sup> The corrin ring bears resemblance to porphyrin rings found in heme and chlorophyll, which are compounds integral to oxygen transport in red blood cells and photosynthesis, respectively. Corrinoids are characterized by a central cobalt atom bonded to four pyrrole nitrogen atoms. In vitamin B12, this cobalt ion is further connected to various groups, including benzimidazole, nucleotide and cyanide.<sup>9</sup> The molecule's upper ligand, known as the cyano group, can be replaced by an adenosyl group to form adenosyl cobalamin (Ado-Cbl) or by a methyl group to create methyl cobalamin (Me-Cbl).<sup>10</sup> Cyanocobalamin (CN-Cbl), despite being a chemically stable form, lacks vitamin activity and is commonly referred to as vitamin B12. As a result of potential health concerns regarding cyanide accumulation in tissues, the use of CN-Cbl has been on the decline. More favourable forms such as Me-Cbl and Ado-Cbl are gaining prominence.<sup>11</sup> Within human cells, enzymatic conversion transforms cyanocobalamin into the active cofactors Me-Cbl and Ado-Cbl, which play crucial roles in cellular metabolism.<sup>12</sup>

## EFFECT AND MECHANISM OF VITAMIN B12 ON THE HUMAN BODY

Vitamin B12, along with other B vitamins, serves as an essential cofactor for enzymes that drive metabolic processes within the body.<sup>13</sup> This vitamin, primarily sourced from animal-derived foods such as meat, eggs and poultry, is originally synthesized by

bacteria.<sup>14</sup> It plays a pivotal role in energy production by participating in the synthesis of red blood cells and the conversion of food into usable energy. Furthermore, vitamin B12 is instrumental in maintaining a healthy nervous system, facilitating the metabolism of fatty acids and amino acids, and regulating the immune response to combat viral infections.<sup>15</sup> The analgesic properties of vitamin B12 may be attributed to its interaction with prostaglandin pathways, including the modulation of cyclooxygenase (COX) enzymes. The comprehensive impact of vitamin B12 on various physiological systems is detailed in Table 1.<sup>21</sup>

Notably, the timely delivery of nutrients to the brain is influenced by dietary intake, and insufficient levels of vitamin B12 have been associated with cognitive decline in individuals over the age of 60 years. This cognitive impairment is linked to diminished myelin integrity, which correlates with an increased presence of white matter lesions in the brain.<sup>22</sup> The digestion of food releases vitamin B12 from its protein-bound foam in the stomach. Free vitamin B12 binds with IF, a glycoprotein produced from the parietal cell of the stomach. The absorption of vitamin B12 is accomplished by the ileum, as shown in Fig. 2, a part of the small intestine.<sup>23</sup> The ileum has a vitamin B12 receptor called cubilin, which forms specific bonds. Vitamin B12 is then released from the IF and binds to another protein called transcobalamin.<sup>24</sup> It is important to note that age significantly influences the absorption and metabolism of nutrients, including vitamins, underscoring the need for age-appropriate nutritional considerations.<sup>25</sup>

### Vitamin B12 in diabetic mellitus

Vitamin B12 deficiency is not linked with diabetic mellitus, but there is a mechanism by which vitamin B12 may affect the development and management of this condition.<sup>26</sup> Diabetes mellitus comprises a group of metabolic illnesses that include insulin resistance at first, decreased insulin secretion, insulin shortage, increased glucose production and improper glucose utilization. Complications of this disease are the leading cause of mortality globally. The cell cannot metabolize carbohydrates because of a lack of insulin, and the body breaks into its protein fat and glycogen, producing glycaemia.<sup>27</sup> Vitamin B12 converts homocysteine to methionine (Fig. 3). Vitamin B12 deficiency can lead to elevated levels of homocysteine, which may contribute to developing

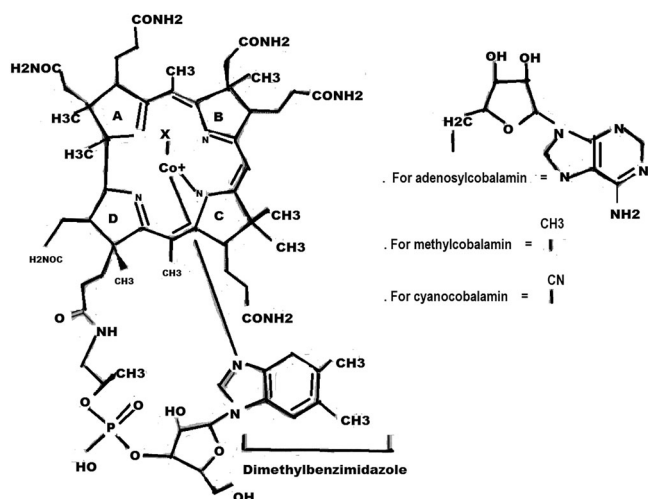
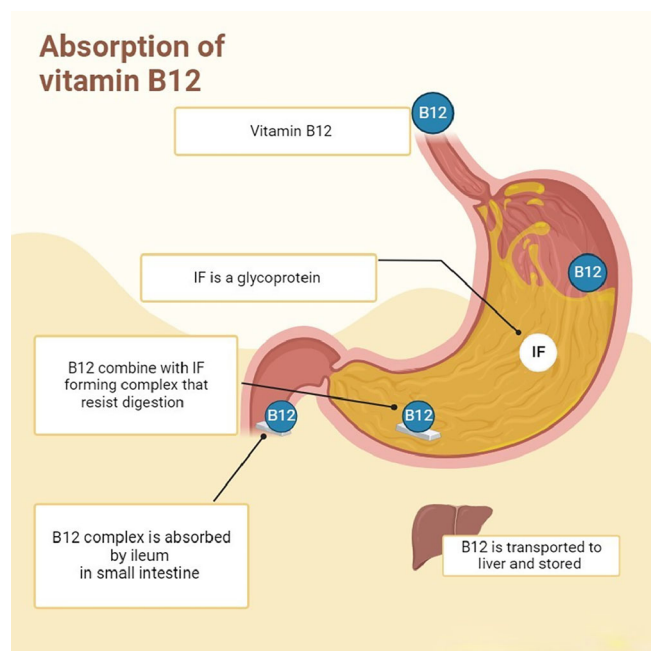


Figure 1. Structure of vitamin B12.

Table 1. Effects of vitamin B12 on various parts of the human body

Body parts and the system	Effects of vitamin B12	Reference
Brain and nervous system	Maintain a myelin sheath that surrounds and protects nerve fibers, which allows proper nerve transmission	Khan <i>et al.</i> <sup>16</sup>
Blood cells	Production of blood cells, a deficiency will lead to anaemia	Singla <i>et al.</i> <sup>17</sup>
Digestive system	Gastric acid production in the stomach helps in the absorption of vitamin B12	Sanz-Cuesta <i>et al.</i> <sup>18</sup>
Small intestine	Alteration in small intestine motility leads to bacterial growth for absorption	White <sup>19</sup>
Liver	The storage of vitamin B12 for years	Edelmann <i>et al.</i> <sup>20</sup>



**Figure 2.** Absorption of vitamin B12.

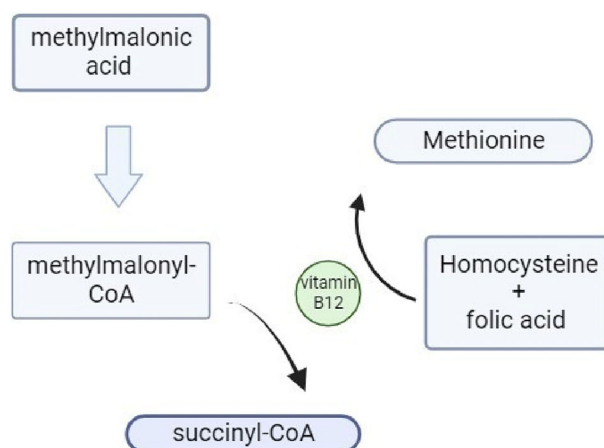
insulin resistance and other related symptoms of diabetic mellitus.<sup>28</sup> Vitamin B12 is essential for the proper functioning of enzymes involved in glucose metabolism, and its deficiency can impair this process, potentially affecting diabetes mellitus by leading to an elevated blood sugar level.<sup>29</sup> Vitamin B12 supplementation may improve insulin sensitivity and glycaemic control in individuals with diabetes mellitus.<sup>30</sup> Although the role of vitamin B12 in diabetes mellitus is not fully understood, there is evidence to suggest that this vitamin may play a beneficial role in the prevention and management of this condition. However, more research is needed to fully elucidate the mechanisms involved and decide the best dosages and duration of vitamin B12 supplementation for individuals with diabetes mellitus.

### Vitamin B12 in pernicious anaemia

Pernicious anaemia occurs when vitamin B12 cannot be absorbed from the food as a result of IF, a protein produced in the stomach responsible for the absorption.<sup>31</sup> This insufficiency is common in adults over 60 years, in women and in those with a family history of autoimmune diseases. Parietal cells play a significant role in why vitamin B12 is not absorbed, whereas autoantibodies play an essential role in pernicious anaemia.<sup>32</sup> Deficiency occurs in lower abdominal tuberculosis when there is involvement of the ileum. Individuals with pernicious anaemia require vitamin B12 supplementation, typically through injections or high-dose oral supplements. This is necessary to maintain adequate levels of vitamin B12 in the body and prevent the development of anaemia.<sup>33</sup> Pernicious anaemia can also be caused by other factors, such as a poor diet or gastrointestinal disorders that affect the absorption of nutrients. Therefore, it is important to consult a healthcare provider to determine the underlying cause of vitamin B12 deficiency and the treatment.<sup>34</sup>

### Vitamin B12 in dyslipidaemia

Vitamin B12 is not linked to dyslipidaemia; however, a study has suggested that low levels of this vitamin are associated with



**Figure 3.** Conversion of homocysteine to methionine by vitamin B12.

cardiovascular risk factors, including dyslipidaemia.<sup>35</sup> Dyslipidaemia is characterized by abnormal lipid levels in the blood, typically involving elevated cholesterol and triglyceride levels. Hyperhomocysteinaemia is a condition characterized by elevated homocysteine levels in the blood.<sup>36</sup> The mechanism by which homocysteine and vitamin B12 deficiency may indirectly contribute to dyslipidaemia is by causing anaemia, which can lead to decreased oxygen delivery to tissues and an increase in cardiovascular risk factors. The exact relationship between vitamin B12 deficiency and dyslipidaemia is not yet fully understood and warrants further investigation.

### Vitamin B12 in obesity

Vitamin B12 helps break down fats and protein and synthesize DNA. Deficiency will lead to slow metabolism, increasing body weight.<sup>37</sup> It plays a vital role in appetite, affecting the level of leptin hormone. Leptin signals the brain when the body has enough food; a low level of vitamin B12 reduces leptin levels, which leads to overeating and weight gain.<sup>38</sup> Vitamin B12 is produced by certain bacteria in the gut, and a healthy gut microbiome is important for maintaining a healthy weight.<sup>39</sup> People with obesity tend to have less diverse gut microbiomes, which may affect the body's ability to absorb vitamin B12 and other nutrients. Low levels of vitamin B12 may be associated with obesity; taking vitamin B12 supplements is not a magic solution for weight loss. A healthy diet and regular exercise are still the most effective ways to achieve and maintain a healthy weight.<sup>40</sup>

### Vitamin B12 in foetal development

Vitamin B12 plays a crucial role in foetal development during pregnancy. Vegans and vegetarians are affected by celiac diseases.<sup>41</sup> A deficiency in vitamin B12 during pregnancy can lead to several complications, including neural tube defects, preterm birth and low birth weight.<sup>42</sup> Low maternal serum vitamin B12 concentration in the first trimester is a risk factor for neural tube defects and poor maternal outcomes such as pre-eclampsia and macrosystemic and neurological deficits.<sup>43</sup> Neural tube defects are birth defects that affect the brain and spinal cord. Vitamin B12 is essential for proper neural tube development, and a deficiency during pregnancy can increase the risk of these defects. To prevent these complications, pregnant women need to ensure that they are getting sufficient vitamin B12 in their diet or through supplementation. The recommended daily intake of vitamin B12

for pregnant women is 2.6 g per day.<sup>44</sup> Good dietary sources of vitamin B12 include meat, fish, dairy products and fortified cereals. Pregnant women who follow a vegetarian or vegan diet may be at higher risk of vitamin B12 deficiency and need to take supplements to meet their daily requirements.<sup>45</sup>

### Vitamin B12 in oxidative stress

When the amount of pro-oxidant chemicals, such as reactive oxygen species, is greater than the capacity of the available antioxidant buffer, oxidative stress is caused.<sup>46</sup> Age-related disorders, where oxidative stress plays a significant role, may develop because of neglected processes over time, suggesting that vitamin B12 has antioxidant effects.<sup>47</sup> Although it plays no direct part in oxidative stress, it indirectly contributes by helping to make glutathione, a vital antioxidant.<sup>48</sup> The body uses the three amino acids, glutamate, cysteine and glycine, to make the tripeptide molecule glutathione. Potent antioxidants such as glutathione work to prevent oxidative cell damage by eliminating harmful chemicals called free radicals.<sup>49</sup> Homocysteine must be converted to methionine with the help of vitamin B12 to create S-adenosylmethionine, a chemical involved in glutathione production. Therefore, vitamin B12 shortage might result in lower glutathione levels and a higher sensitivity to oxidative stress.<sup>50</sup> The digestive system cells responsible for absorbing vitamin B12 might also be harmed by oxidative stress, which will further lower vitamin B12 levels.<sup>51</sup>

### CLINICAL STUDIES

Several epidemiological studies and animal models have shown a link between the importance of vitamin B12 and various aspects of the metabolic syndrome. European (27%) and South Indian (32%) patients with type 2 diabetes have a low incidence of high B12 levels.<sup>52</sup> There is no international consensus on the lower limit of vitamin B12 that defines adult and pregnancy B12 deficiency. However, there is a consensus that it should be between 120 and 220 pmol L<sup>-1</sup> (the high threshold during pregnancy) and the upper limit between 650 and 850 pmol L<sup>-1</sup>.<sup>53</sup> Metformin consumption in type 2 diabetes mellitus patients decreases vitamin B12 availability and absorption, which leads to vitamin B12 deficiency.<sup>54</sup> Supplementation of methyl cobalamin and cyanocobalamin is aiding in treating COVID-19, especially in patients with vitamin B12 deficiency.<sup>55</sup> When combined with other members of the B vitamin family or taken alone, vitamin B12 positively affects brain atrophy, inflammation and cognitive function in elderly people who are not cognitively impaired or in individuals with mild cognitive impairment.<sup>56</sup> Compared with either vitamin B12 or folic acid alone, the combined intervention with vitamin B12 and folic acid performed significantly better for all endpoints.<sup>57</sup> Vitamin B12 and folic acids showed therapeutic responses for Alzheimer's disease.<sup>58</sup> Folic acid, vitamin B12 and vitamin B6 reduce the effects of para-oxonase 1 on cognition in people with mild cognitive impairment.<sup>59</sup> Serious haematological effects must be treated with drugs. Current treatment comprises oral or parenteral enhancements of cyanocobalamin; however, the parenteral route is not well accepted, and the oral route is avoided in patients with malabsorption syndrome.<sup>60</sup> Alternatives such as topical treatments have been proposed, but the hydrophilicity and low molecular weight of cyanocobalamin prevent it from spreading through the skin. Molecules larger than 500 Da can be trans dermally absorbed through lipid vesicles.<sup>61</sup> Older people to assess the

contribution of vitamin B12 deficiency to the development of oxidative stress. The mean  $\pm$  SD age of the 51 participants with vitamin B12 deficiency was 45.76  $\pm$  15.70 years, and 15 (29.5%) of them were female.<sup>62</sup> Thirty-seven (72.5%) patients were vegetarians, and 11 (24.4%) smoked cigarettes and drank alcohol. Thirty-one patients (60.7%) in the study group had symptoms of non-subacute combined degeneration (SACD) when first diagnosed. Twenty (39.2%) of the patients had SACD, 14 had Myel cognitive disorders and six had neuropsychiatric abnormalities in addition to the standard symptoms and signs of vitamin B12 deficiency.<sup>63</sup> Maternal lack of nutrients is related to low birth weight and expanded perinatal bleakness and mortality<sup>64</sup>. The relationship between B12 status and oxidative stress consistently shows that a lower B12 status is associated with higher pro-oxidants and more inadequate antioxidants, both overall and for subclinical B12 deficiency compared to normal B12 status.<sup>18</sup> However, causality cannot be confirmed because of a lack of prospective research, consensus on proper biomarkers and B12-specific interventions. Clinical studies on obesity, insulin resistance, dyslipidaemia, cardiovascular diseases, reducing pain, Alzheimer's, type 2 diabetics, cardiometabolic risk lipid metabolism, lower back pain conditions, neuropathy, oxidative stress, antioxidant activities, and bone mineral density in pernicious anaemia are shown in Table 2.

### FOOD APPLICATIONS

Commodity food fortification has been acknowledged as a successful strategy for addressing micronutrient deficits. Vitamin B12 is naturally present in meat, fish and eggs.<sup>71</sup> Vitamin B12 stability in milk depends on how much the milk has been heatedly processed, with losses of up to 20 and 35 g kg<sup>-1</sup> occurring after spray drying and milk sterilization, respectively.<sup>72</sup> The content of CN-Cbl was unaffected by baking with straight or sponge dough; CN-Cbl (23 g kg<sup>-1</sup>) degradation was brought on by the sourdough baking process. CN-Cbl degradation ranged from 23 g kg<sup>-1</sup> loss at 140 °C to almost complete degradation at 194 °C, but screw speed and feed rate had less impact on CN-Cbl stability.<sup>73</sup> The extent of CN-Cbl degradation was determined by die temperature. Vitamin B12 steadiness in food relies upon the cooking temperature and time, as well as the presence of other food ingredients.<sup>74</sup>

In extrusion, the temperature of the die had a significant impact on the stability of vitamin B12. The steadiness of vitamin B12 was unaffected by screw speed and feed rate. The best physio-functional properties were obtained through extrusion at 168 °C, with 229 rpm and 4.6 kg h<sup>-1</sup>. Vitamin B12 was maintained most effectively (77 g kg<sup>-1</sup>) when extruded at 140 °C, with 150 rpm and 4 kg h<sup>-1</sup>. The physio-functional properties were improved by adding carboxymethyl cellulose (5 g kg<sup>-1</sup>).<sup>73</sup> Over the past decade, the availability and consumption of food supplements and fortified foods have steadily increased worldwide as a result of increased health awareness, an ageing population, lifestyle changes and rising healthcare costs<sup>75</sup>. The stabilization of vitamin B12 is primarily restricted to CN-Cbl. However, given that Ado-Cbl and Me-Cbl have lower stability than CN-Cbl, such research would benefit these three vitamin B12 forms more. A large number of the tested fortified foods (31%) and food supplements (11%) have vitamin B12 levels above the highest acceptable tolerance (150%), showing the need for more stringent quality control of these products.<sup>76</sup>

**Table 2.** Clinical studies for different diseases and conditions

Diseases and conditions	Studies	Main findings	Reference
Obesity	Adult Wistar rats were fed a B12-restricted diet (control, 0.010 mg kg <sup>-1</sup> B12 vs. B12-restricted, 0.006 mg kg <sup>-1</sup> B12) during the maternal or postnatal period	Alter the offspring's lipid metabolism and predict higher visceral adiposity	Kumar <i>et al.</i> <sup>64</sup>
Insulin resistance	Maternal B12, folate and methionine restriction (control versus restricted: At the time of conception, B12 (1000.5 pm vs. 198 pM), folate (6.90 nM vs. 4.42 nM) and methionine (39.1 vs. 30.8 mM) were found to increase insulin resistance and raise blood pressure in sheep models' offspring	The lower availability of S-adenosyl methionine, a well-known methyl donor, which is essential in epigenetic modulations underpinning the development of insulin resistance, could explain the decreased methylation of DNA	Sinclair <i>et al.</i> <sup>65</sup>
Dyslipidemia	C57 BL/6 mice with low plasma B12 levels at 12 weeks (145 pg mL <sup>-1</sup> compared to 548 pg mL <sup>-1</sup> control) and 36 weeks (123 pg mL <sup>-1</sup> compared to 522 pg mL <sup>-1</sup> control)	Higher plasma triglycerides, cholesterol and pro-inflammatory markers such as tumour necrosis factor, interleukin-1b, and interleukin-6, as well as lower adiponectin concentrations	Shampa <i>et al.</i> <sup>66</sup>
cardiovascular diseases	Grown-up male Sprague-Dawley rodent model treated with testosterone enanthate (0.5 mg/100 g) and B12 (500 µg kg <sup>-1</sup> )	Tremendous changes with fringe cortisol and relationship with vascular brokenness	Lodhi & Panchal <sup>67</sup>
Mechanism in Reducing Pain	Intraperitoneal injections of vitamin B12 (0.87, 1 and 1.77 mg kg <sup>-1</sup> ) were made. The anti-nociceptive effects against acute pain were investigated using the hot-plate and writhing tests. The hot-plate test investigated the chronic discomfort 14 days following sciatic nerve ligation. As a positive control, morphine (10 mg kg <sup>-1</sup> ) was used. Utilizing, respectively, compressed cotton implantation and xylene-induced ear edoema, the anti-inflammatory effects of vitamin B12 against acute and chronic inflammation were studied	A methyl-deficient diet without vitamin B12, folate, or choline caused a significant upregulation of COX2 in the intestines after exposure to dextran sodium sulfate in rats with colitis caused by dextran sodium sulfate. Vitamin B12 may play a role in maintaining COX2 levels under control during inflammatory conditions	Hosseinzadeh <i>et al.</i> <sup>68</sup>
Alzheimer's (cognitive impairments)	Patients with stable conditions and a clinical diagnosis of probable Alzheimer's disease (n = 120). The intervention group (n = 60, folic acid 1.2 mg day <sup>-1</sup> + vitamin B12 50 g day <sup>-1</sup> ) and the placebo group (n = 60) were randomly assigned to the participants. At baseline and 6 months later, cognitive function, blood folate, vitamin B12, one carbon cycle metabolite and inflammatory cytokine levels were assessed	When taken daily, folic acid, vitamin B12, and vitamin B6 reduce the negative effects of paraoxonase on cognition in people with mild cognitive impairment	Chen <i>et al.</i> <sup>69</sup>
Type 2 diabetics, cardiometabolic risk and lipid metabolism	Pregnant women with low B12 (150 pmol L <sup>-1</sup> ) had higher obesity and a higher chance of developing type 2 diabetes. Increased insulin resistance was linked to low B12 levels (180 pmol L <sup>-1</sup> ) in pregnant white Caucasian women without gestational diabetes In the North Indian population, low HDL and hyperhomocysteinemia correlated with low B12 levels (220 pg mL <sup>-1</sup> ). Patients with cardiovascular disease and/or renal diseases who took B12 supplements experienced a lower incidence of stroke	Low B12 status has been linked to greater lipids, obesity, and an increased risk of insulin resistance, type 2 diabetes, and cardiovascular disease in children, adolescents, and pregnant women. Adverse maternal programming causes low B12 moms to have babies who appear to have high levels of adiposity and insulin at birth, which could put them at risk of having cardiometabolic illnesses later in life	Boachie <i>et al.</i> <sup>35</sup>
Lower back pain conditions and neuropathy	(> 100 µg dose <sup>-1</sup> ) Vitamin B12 was induced in rats	Cyanocobalamin, regarded as one of the least effective forms of vitamin B12 for treatment, appeared to quickly alleviate chronic low back pain. Oral Me-Cbl cramps were reduced by 85%, pain was reduced by 70%, and 2-point discrimination was improved by 33%	Bruins <i>et al.</i> <sup>10</sup>

**Table 2.** Continued

Diseases and conditions	Studies	Main findings	Reference
Oxidative stress and antioxidant activities	The oxidative stress markers in patients with B12 deficiency compared to healthy volunteers. Fifty-one individuals with low serum B12 levels (age 45.78 ± 2.19 years, 70.6% male) 53 healthy participants (age 44.28 ± 2.20 years; 77.8% men).	It had antioxidant activity. Compared to the non-SACD vitamin B12 deficiency group, SACD patients had significantly more oxidative stress and lower antioxidant levels	Edelmann et al. <sup>20</sup>
Bone mineral density (BMD) in pernicious anemia	Average BMD measures for four categories of vitamin B12 concentrations were estimated using commonly used cut-offs, analysis of covariance, adjusted for age, body mass index, physical activity score for the elderly (i.e. PASE), alcohol consumption, smoking, total calcium and vitamin D intake, and bone measurement season, and, for women, menopause status and current oestrogen use	The average BMD of adults with vitamin B12 concentrations below 148 pM was lower than those with vitamin B12 levels above this threshold	Macédo et al. <sup>20</sup>

## OTHER UTILIZATIONS

Besides its role in keeping a healthy nervous system and red blood cell formation, vitamin B12 has other non-health-related uses, including industrial, cosmetic, animal feed and environmental uses.<sup>77</sup> Vitamin B12 is a source of cobalt in producing chemicals such as adhesives, plastics and cleaning agents.<sup>78</sup> Vitamin B12 is typically produced using fermentation methods, which involve the growth of *Paracoccus denitrifices*. The bacteria produce vitamin B12 as a by-product of their metabolism, which can then be isolated and purified in industrial applications<sup>79</sup>. Vitamin B12 is mostly used to make mixed animal feed, especially for poultry, processed foods, vitamin pills and other products<sup>80</sup>. Pigs, poultry and calves are the main animals for which vitamin B12 is added to the diet, indicating that, unlike ruminants, the microbiota of these animals does not produce enough of the coenzyme on their own<sup>81</sup>. In Europe and the USA, the dose range for all animal diets is between 10 and 30 mg t<sup>-1</sup>. More than 30 tonnes of biotechnological vitamin B12 is produced annually in food, feed and medicinal applications.<sup>82</sup> *Propionibacterium shermanii* and *Pseudomonas denitrifices*, the two main industrial strains that completely replace chemical synthesis in the biosynthesis of cobalamin and include around 30 enzymatic steps, are exploited to produce most of the vitamin B12 used commercially.<sup>83</sup> Vitamin B12 has been shown to have antioxidant and anti-inflammatory properties, which can help improve skin texture, reduce fine lines and wrinkles, and promote overall skin health, and vitamin B12 is a popular ingredient in cosmetic products, particularly in anti-ageing creams and serums, and also provides evidence for its potential benefits for skin health.<sup>10,84</sup>

## CONCLUSIONS

Vitamin B12 is found in supplements and fortified meals in its free form, which may make them easier to absorb. Vitamin B12 in the form of medicine is used for treatment of deficiencies and cases of malabsorption, as well as for elderly people and vegetarians. CN-Cbl is the most used form for treatments, although further research is needed for the effective form of vitamin B12 for use in treatments. Studies suggest that vitamin B12 supplementation may help individuals with deficiencies and those with certain medical conditions, such as pernicious anaemia. However, research on the efficacy of vitamin B12 supplementation for other conditions has yielded conflicting results. In conclusion, although vitamin B12 is essential for proper bodily function, more research is needed to fully understand the effects of supplementation in the prevention and treatment of various health conditions. Those at risk of vitamin B12 deficiency should consult their healthcare provider to determine whether supplementation is necessary. Research is also needed to decide the dosage and stability of vitamin B12 for different diseases, as well as the strength of various forms of vitamin B12 to help manufacture fortified foods, supplements and medicines of the highest quality.

## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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