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KANGEN UKON SIGMA SOFTGELS LITERATURE REVIEW REPORT

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PRODUCT NAME : KANGEN UKON SIGMA SOFTGELS

1.0 INTRODUCTION

1.1 Non-Clinical Studies & Clinical Trials

The health function or efficacy of a health supplement is typically substantiated through rigorous scientific methods, including:

• **Non-Clinical Studies**: These are preclinical tests often conducted *in vitro* (in a lab setting) or *in vivo* (in animals) to assess the biological activity and safety of the supplement's ingredients. They provide initial data on pharmacodynamics (what the supplement does to the body), pharmacokinetics (how the body processes the supplement), and toxicology.

• **Clinical Trials**: These are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way researchers find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people. For health supplements, clinical trials help to:

- Confirm the findings from non-clinical studies.
- Evaluate the efficacy of the supplement in the target population.
- Monitor side effects and ensure the product is safe for human consumption.
- Determine the optimal dosage and administration route.

The results from the non-clinical studies and clinical trials are critical for making claims about the health benefits of the supplement. They also provide valuable information to healthcare professionals and consumers, helping them make informed choices about supplement use. It is important that these studies are well-designed,

executed according to strict regulatory standards, and peer-reviewed to ensure reliability and credibility of the data.

Nevertheless, conducting non-clinical studies and clinical trials for health supplements indeed comes with several disadvantages, including:

i) Time-Consuming: The process from non-clinical studies to clinical trials and then to market can take several years. This is due to the extensive research, development, and regulatory approval required.

ii) High Costs: The financial investment is significant. Clinical trials, in particular, are costly due to the need for specialized staff, equipment, and resources to ensure compliance with regulatory standards.

iii) Regulatory Hurdles: Obtaining regulatory approval can be a complex and lengthy process. Each phase of clinical trials requires approval, and any adverse events must be thoroughly investigated, which can delay progress.

iv) Participant Recruitment: There may be a decreasing willingness of patients or participants to be involved in clinical trials, which can affect recruitment and the generalizability of the trial results. Thus, recruiting a sufficient number of suitable participants for clinical trials can be challenging and may lead to delays.

v) Ethical Considerations: Ensuring ethical conduct, informed consent, and participant's safety require meticulous planning and oversight, which can add to the complexity and duration of trials.

These challenges highlight the need for careful planning, adequate funding, and efficient management to successfully conduct research on health supplements.

1.2 Literature Review

The efficacy results obtained from the non-clinical studies and clinical trials can actually be obtained by conducting a literature review on the active ingredients of the health supplement. In fact, conducting a literature review on the active ingredients of a health supplement is a critical step in substantiating the health function or efficacy of a health supplement.

Literature review for the active ingredients of health supplement involves a comprehensive review of non-clinical studies and clinical trials conducted previously on similar active ingredients to understand the efficacy of the active ingredients.

The reasons why the literature review should be conducted on the active ingredients of the health supplement include:

• Validation of Results: A literature review can validate the findings by comparing them with existing research and data. If the results are consistent with the literature, it strengthens the credibility of the efficacy claims.

• Contextual Understanding: It provides a broader context for understanding the effects of the active ingredients, including historical use, traditional medicine perspectives, and previous scientific investigations.

• Safety Profiling: By reviewing the literature, researchers are able to compile a comprehensive safety profile of the active ingredients, which is essential for consumer protection.

• Dose-Response Relationship: Literature reviews can help in identifying the dose-response relationship of the active ingredients, which is crucial for determining the effective dosage of the health supplement.

• Mechanism of Action: Understanding the mechanism of action of the active ingredients through literature can explain how and why a health supplement is effective, which is important for both healthcare professionals and consumers.

• Identification of Research Gaps: It can reveal gaps in the current knowledge and suggest areas for future research, leading to the continuous improvement of health supplement.

In essence, literature review serves as a bridge that connects experimental findings with the vast body of existing scientific knowledge, ensuring that the health supplement claims are well-founded and reliable. It is an integral part of the evidence-based approach to supplement development and marketing.

2.0 LITERATURE REVIEW CONDUCTED ON THE ACTIVE INGREDIENTS

The health benefits and efficacy of Kangen Ukon Sigma Softgels have been evaluated through literature reviews on the 9 active ingredients contained in the product.

Kangen Ukon Sigma Softgels is a dark brown color, oval shape, 13 mm length, 450 mg softgel. Kangen Ukon Sigma Softgels consist of a unique blend of natural ingredients and mixed essential vitamins, each selected for their potential health benefits. This comprehensive formulation contains the natural ingredients of Turmeric Powder, Squalene, Fish Oil and a spectrum of essential vitamins, namely, Riboflavin, Niacinamide, Thiamine Mononitrate, Ascorbic Acid, Folic Acid and Cyanocobalamin. The active compounds in Kangen Ukon Sigma Softgels have been the subject of extensive research, highlighting their roles in promoting health. This literature review report delves into the scientific evidence supporting the efficacy of each ingredient, exploring their synergistic effects on human health. From the antioxidant and anti-inflammatory properties of Turmeric Powder to the cardioprotective effects of Fish Oil, we will examine how Kangen Ukon Sigma Softgels may contribute to overall well-being and the management of various health conditions.

2.1 Turmeric Powder

In a 450 mg Kangen Ukon Sigma Softgel, 120 mg of Turmeric Powder is formulated and incorporated in the softgel making it the main active ingredient in Kangen Ukon Sigma Softgels.

Turmeric Powder is obtained from the rhizome of Curcuma longa L. from the Zingiberaceae family. It is widely used in the Middle East and Asia, not only to impart a distinctive flavor to foods, but also to provide health benefits. Turmeric has been traditionally used in Asian countries as a medical herb due to its antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties (Benzie, 2011, Chapter 13).

The components of Turmeric are collectively known as curcuminoids. Curcuminoids have a central role and may compose up to 10% of dry Turmeric Powder. This category mainly comprises curcumin, dimethoxy-curcumin, and bisdemethoxycurcumin. Curcumin is the most biologically active curcuminoid in turmeric which can compose 62–90 mg/g of commercial turmeric products (El-Saadony et al., 2023).

Curcumin is a hydrophobic polyphenol that can cross the blood-brain barrier (El-Saadony et al., 2023). Curcumin has been used as a potential therapeutic agent for various neurological disorders, such as dementia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and Huntington's disease, due to its antioxidant, anti-inflammatory, and anti-protein aggregating abilities (Ye and Zhang, 2012; Wu et al., 2013; Song et al., 2016; Teter et al., 2019; Salehi et al., 2020a). Curcumin was investigated heavily as a treatment for Alzheimer's disease. It stimulated neurogenesis via the Notch and Wnt/β-catenin pathways, diminished the secretion of proinflammatory cytokines, and led to the deactivation of GSK-3β, which in turn reduced β-amyloid (Aβ) production and the buildup of plaques by downregulating the ROS/JNK pathway (Shahbaz et al. 2022).

Curcumin is able to promote its antioxidant activity by scavenging a variety of reactive oxygen species as superoxide radicals, hydrogen peroxide, and nitric oxide radicals and by inhibiting lipid peroxidation (Ak & Gülçin, 2008). A systematic review and meta-analysis of randomized control data related to the efficacy of supplementation with purified curcuminoids on oxidative stress parameter indicated a significant effect of curcuminoids supplementation on all investigated parameters of oxidative stress including plasma activities of superoxide dismutase and catalase, as well as serum concentrations of glutathione peroxidase and lipid peroxides (Sahebkar et al., 2015). Substance with antioxidant activity has several benefits for the human body, primarily due to its ability to neutralize free radicals, which are unstable molecules that can cause cellular damage. The key benefits of the antioxidants are: i) Protection against chronic diseases since antioxidants can prevent or slow cell damage caused by free radicals, potentially reducing the risk of inflammation and various health issues such as heart disease, cancer, arthritis, stroke, and respiratory diseases; ii) Support for heart health since antioxidants may help to lower the risk of heart disease by preventing oxidative stress that can lead to atherosclerosis, a condition characterized by the hardening and narrowing of the arteries.

Many investigations have clarified that curcumin has potent anti-cancer impacts via suppressions of angiogenesis formation of new blood vessels from the preexisting vessels (Chatterjee et al., 2021). It also suppresses cancer cell metastasis and induces cancer cell apoptosis (Sharifi-Rad et al., 2020).

Curcumin has been shown to improve symptoms and delay disease cycles in rheumatoid arthritis patients by inhibiting mitogen-activated protein kinase family, extracellular signal-regulated protein kinase, activator protein-1, and nuclear factor κB signal pathway in rheumatoid arthritis (Pourhabibi-Zarandi et al., 2021). Curcumin treated by rheumatoid arthritis patients with taking 250-1500 mg/day over 8-12 weeks can improve dysfunctional immune cells (including TH1, TH17, Treg and B cells) and reduce the clinical symptoms of the disease (Mohammadian Haftcheshmeh et al., 2021).

Curcumin has been shown to have anti-atherosclerotic activity through its anti-inflammatory and anti-oxidant mechanisms (Singh et al., 2021). According to a study conducted on smooth muscle cells isolated from the thoracic aorta of rats and stimulated for 24 hours with Angiotensin II, which plays a significant role in the development of atherosclerotic plaques, treatment with curcumin causes decrease in Angiotensin II induced production of proinflammatory cytokines in a concentration-dependent manner (Hansson, 2005). Low-density cholesterol (LDL) oxidation, also plays an important role in the development of atherosclerosis. Curcumin has also been shown to be an effective antioxidant by preventing the oxidation and modification of LDL (Mahfouz et al., 2009).

It was shown that curcumin can inhibit pro-inflammatory transcription factors, reduce the proinflammatory cytokines, down-regulate enzymes such as 5-lipoxygenase and COX-2 and inhibit the mitogen activatedprotein kinases (MAPK) and pathways involved in nitric oxide synthase (NOS) enzymes synthesis (Aggarwal and Sung, 2009; Panahi et al., 2014a; Panahi et al., 2014b; He et al., 2015; Machova Urdzikova et al., 2015). The ability of curcumin to inhibit pro-inflammatory transcription factors is important because it plays a crucial role in the management of inflammation, which is a fundamental response of the immune system to injury or infection. However, when inflammation becomes chronic, it can lead to various diseases and conditions. For example, chronic inflammation is associated with a range of diseases, including asthma, arthritis, and inflammatory bowel disease. Besides, autoimmune diseases occur when the immune system mistakenly attacks the body's own tissues. Inhibiting pro-inflammatory transcription factors can help to manage the inappropriate immune response in these diseases. By managing inflammation and its symptoms, these curcumin can significantly improve the quality of life for individuals with chronic inflammatory conditions.

Sharma et al. (2007) noted that 1.5 g of Turmeric Powder per day (about 150 mg of curcumin, average consumption in India) did not exhibit any side effects in humans. With a long-established safety record, curcumin has been found to be quite safe in

animals and humans, even at doses up to 8 g/day. Consequently, this substance was declared as GRAS by the FDA (Sharifi-Rad et al. 2020).

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2.2 Squalene (SQ)

Squalene (SQ) is the second main ingredient in Kangen Ukon Sigma Softgels, containing 100 mg of squalene in each 450 mg softgel. SQ is a natural organic compound originally obtained for commercial purposes primarily from shark liver oil, though it can also be found in smaller quantities in some vegetable oils. Chemically, it is a triterpene, a type of hydrocarbon compound that is widespread in nature. Historically, SQ gained attention for its various applications, particularly in the pharmaceutical and cosmetic industries. In medicine, it has been used as an adjuvant in vaccines to enhance the immune response (Suli et al., 2004). Additionally, it has been explored for its potential health benefits. *In vitro* and *in vivo* studies unraveled antioxidant properties of SQ by reducing stress-induced intracellular reactive oxygen species (ROS). Moreover, SQ decreases cytokine secretion and leads to an overall reduction in pro-inflammatory genes in immune cells, which suggests a protective role against uncontrolled inflammatory response. Furthermore, as SQ is naturally occurring oil, it has been regarded as a biocompatible drug carrier.

It is known that sharks are rich sources of SQ and more than 40% of shark liver contains SQ. It has been reported that absence of cancer in sharks is associated with such high SQ levels (Liu et al., 1976; Mathews, 1992). SQ is thought to inhibit carcinogenesis by inhibiting farnesylation of Ras oncoprotein and restricting transformation of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) into mevalonate; modulating biosynthesis and functions of xenobioticmetabolizing enzymes; scavenging free radicals (Smith, 2000). It has been reported that SQ emulsions given simultaneously with anti-cancer drugs provide favorable effects either directly or indirectly by enhancing efficacy of anti-cancer drugs (Yarkoni & Rapp, 1979; Pimm et al., 1980; Nakagawa et al., 1985).

Research by Cardeno et al. (2015) showed that SQ had great potential in regulating inflammation. SQ takes part in regulating the activation pathways of neutrophils, monocytes, and macrophages, effectively targeting anti-inflammatory factors to exert

its biological functions. Sánchez et al. (2015) demonstrated that dietary supplementation with 25 and 125 mg/kg of SQ significantly alleviated dexton sulphate sodium (DSS)-induced colitis injury in weaned mice by inhibiting the phosphor relation of the mitogen-activated protein kinases (MAPK) and NF-kB signaling pathways. In addition, SQ down-regulated the expression of COX-2 and iNOS, which helped to repair the damaged intestinal mucosal epithelial barrier and reduce the inflammatory response (Cardeno et al., 2015; Chang et al., 2015).

Study showed that adding 2% SQ to the diet significantly reduced levels of cholesterol, triglycerides, and free fatty acids in rat plasma and heart tissue, reducing fat deposition in the heart (Farvin et al. 2005). SQ can accelerate the transport of cholesterol, triglycerides, and free fatty acids in plasma and the heart, promoting lipid metabolism (Chan et al., 1996). In addition, SQ can regulate cholesterol synthesis by inhibiting the key enzyme HMG-CoA reductase levels in the cholesterol synthesis pathway through negative feedback regulation, which is similar to the mechanism of action of statins (Bhilwade et al., 2010).

When membrane damage occurs, SQ can repair the injured membrane, and exert its antioxidant effect (Nurfatimah et al., 2021, Kim & Karadeniz, 2012). The mechanism is hypothesized to occur as SQ has an abundant double-bond structure and is lipid-soluble, which rapidly fills in the damaged cell membrane structure (Reddy & Couvreur, 2009). SQ can bind with hydrogen ions present in water, penetrate into cells, and enhance cellular metabolic functions (Reddy & Couvreur, 2009). Studies have shown that SQ has a strong scavenging effect on singlet oxygen, and the effect is significantly higher than other lipids in the animal body (Auffray, 2007). At the same time, SQ can significantly reduce the transmission efficiency of free radicals on the skin and protect cell DNA from damage (Warleta et al., 2010).

SQ emulsions are frequently used to carry vaccines and drugs into the body (Reddy & Couvreur, 2009; Huang et al., 2009; Fox, 2009). SQ used for this purpose bears the role of immunological adjuvant and remains safe and non-toxic for the host while enhancing

immune response (Mesa & Fernandez, 2004). MF59 (Novartis), AS03 (GSK), and AF03 (Sanofi) are oil in water (o/w) emulsions that contain SQ droplets (Nguyen-Contant et al., 2021; Tregoning et al., 2018). All three are approved for use in both seasonal and pandemic influenza vaccines. Studies in mice and non-human primates showed that, besides their role as antigen carriers, SQ-based adjuvants enhance both innate and adaptive immune responses (Calabro et al., 2011; Dupuis et al., 1999; Mosca et al., 2008).

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2.3 Fish Oil

The third main ingredient in Kangen Ukon Sigma Softgels is Fish Oil. Each 450 mg softgel contains 38.96 mg of Fish Oil. Fish Oil is derived from the tissues of oily fish. It is rich in omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are essential nutrients with numerous health benefits. Omega-3 fatty acids are considered essential because the human body cannot produce them on its own and must obtain them through diet. These fatty acids play crucial roles in various bodily functions, including brain function, cardiovascular health, inflammation regulation, and eye health. Fish Oil gained popularity as a health supplement due to extensive research supporting its potential benefits.

Omega-3 PUFAs may increase antioxidant activity, such as superoxide dismutase (SOD), guaiacol peroxidase (GPX), catalase (CAT), and glutathione (GSH), enhancing the resistance to free radical attack and reducing lipid peroxidation and oxidative stress (Shati & El-Kott, 2021; Veras et al., 2021; Lluís et al., 2013). Diet with a 1:1 ratio of EPA/DHA improved the oxidative stress parameters (SOD and GPX in erythrocytes) and plasma antioxidant capacity (Lluís et al., 2013).

Studies in healthy subjects and cardiovascular high-risk patients suggested that a supplement of Omega-3 PUFAs may be an effective treatment to reduce inflammation (Vors et al., 2017; Yang et al., 2020; Li et al., 2014). The resolvin E series is synthesized by EPA, which can effectively reduce the tracking of leukocytes to inflammatory sites, promote the clearance of inflammatory cells, and inhibit the production of cytokines (Serhan, 2014). Resolvin D1 synthesized by DHA may induce the transformation of anti-inflammatory M2 macrophages, which reduced the pro-fibrotic genes and decreased collagen deposition, thereby reducing post-MI fibrosis and, thus, stabilizing the extracellular matrix (Kain et al., 2015).

Experimental studies have shown that Fish Oil may exert its antiarrhythmic effect by the direct influence of a cardiac electrophysiological character or indirect regulation of

autonomic nerve function (Tribulova et al., 2017; Xin et al., 2013; Suenari et al., 2011). An animal study showed that supplementing diets with high-dose Fish Oil may enhance cardiac contractile efficiency and improve cardiac function (Macartney et al., 2021). Omega-3 PUFAs may inhibit sarcolemmal ion channels, stabilize electrical activity, and prolong the relative refractory period of the cardiomyocytes (Tribulova et al., 2017).

Lipid metabolism disorder as an important part of atherosclerosis progression may also be regulated by Fish Oil. Omega-3 PUFAs may decrease the activity of sterol receptor element-binding protein-1c, which is the key factor in controlling lipogenesis, resulting in the reduction of very low-density lipoprotein (VLDL) and triglyceride (TG) (Kromhout et al., 2012, Sampath & Ntambi, 2005). Furthermore, Fish Oil has been shown to reduce the remnant lipoproteins (RLP) and post-prandial lipemia after fatty meals in patients with hyperlipidemic (Nakamura et al., 1999).

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2.4 Riboflavin

Riboflavin is one of the mixed essential vitamins that contained in Kangen Ukon Sigma Softgels. Each 450 mg softgel contains 5 mg of Riboflavin. Riboflavin, also known as vitamin B2, is a water-soluble vitamin that plays a crucial role in various physiological functions within the human body. It belongs to the group of B vitamins, which are essential for metabolism, cellular function, and overall health. Riboflavin is naturally present in a variety of foods, including dairy products, meat, fish, eggs, nuts, and leafy green vegetables. It's also commonly added to fortified foods and supplements. As a water-soluble vitamin, it must be obtained through dietary sources, and its deficiency can lead to a range of health issues.

It has been demonstrated that supplementation of Riboflavin significantly extended the lifetime and strengthened the reproduction of fruit flies via enhancing the activity of antioxidant enzymes (Zou et al., 2015). Riboflavin also activates the synthesis of a normal extracellular matrix and reduces reactive oxygen species (ROS) levels in keratoconus (Cheung et al., 2014). Riboflavin was used for its potent antioxidant and anti-inflammatory effects in the ischaemic liver protecting hepatic parenchymal cells against ischemia-reperfusion injury (Sanches et al., 2014).

Riboflavin can significantly protect against oxidant-mediated inflammatory injury in the lungs of Long-Evans rats caused by cobra venom factor or IgG immune complexes, or ischemia-perfusion (Seekamp et al., 1999). Riboflavin has also been reported to have a protective role in focal ischemia with decreasing brain injury and edema formation in rats (Betz et al., 1994). Riboflavin also has cardio-protective effects in isolated rabbit cardiomyocytes, reducing elevated ferrylmyoglobulin induced by cardiac re-oxygenation damage. This effect is mediated by Flavin reductase (Mack et al., 1995).

Riboflavin activates phagocytic activity of neutrophils and macrophages, and stimulates the multiplication of neutrophils and monocytes (Araki et al., 1995). Riboflavin administration affects neutrophil migration, inhibiting the infiltration and accumulation

of activated granulocytes into peripheral sites, which may lead to a decreased inflammatory influx and, thereby, a decrease in inflammatory symptoms (Verdrengh & Tarkowski, 2005). Riboflavin suppressed T-cells infiltration and donor-reactive alloantibody formation during the early period after allotransplantation (Iwanaga et al., 2007).

There have been several articles reporting results of randomized controlled trials of Riboflavin on risk of cancer incidence. The study carried out by Machado et al. (2013) demonstrated a strong inhibitory effect of Riboflavin on melanoma metastasis formation in lung of animal model. In female non-smokers, a higher intake of Riboflavin was correlated with a decrease the risk of lung cancer. The Riboflavin intake of 1.2 mg per day was associated with a lower risk of developing lung cancer compared to an intake of 0.52 mg per day (Takata et al., 2012). The deficiency of Riboflavin increases the risk of cancer, while others propose an attenuating effect of some carcinogens (Rivlin et al., 1973).

Riboflavin contributes to blood cells formation as it plays a role in erythropoiesis, improves iron absorption and helps in the mobilization of ferritin from tissues (Boisvert et al., 1993). The concentration of hemoglobin was able to be increased by Riboflavin supplementation. In an animal model, Riboflavin was also shown to enhance iron absorption (Powers et al., 1993), while Riboflavin deficiency increases the rate of gastrointestinal loss of iron and decreases the mobilization of iron from its stores (Powers et al., 1983).

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2.5 Niacinamide

Kangen Ukon Sigma Softgels include Niacinamide among their blend of essential vitamins. Each softgel, weighing 450 mg, provides 1 mg of Niacinamide. Niacinamide, also known as nicotinamide or Vitamin B3, is a water-soluble vitamin that plays a crucial role in various physiological functions within the body. It is a versatile compound with a wide range of benefits for both health and skincare. It is a key component in the synthesis of NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate), which are coenzymes involved in numerous metabolic pathways, including energy production and cellular repair.

Ingestion of nicotinamide, prevents lipid peroxidation and normalizes the reduced antioxidants and antioxidant enzymes in experimental animal models (Nadzhimutdinov et al., 1993; Legon'kova et al., 1997; Velykyi et al., 1996). Kamat et al. showed that nicotinamide scavenged singlet oxygen and inhibited lipid peroxidation of rat liver microsomes induced by the photosensitized reaction of methylene blue irradiated with visible light in the presence of oxygen. They also showed that nicotinamide inhibited lipid peroxidation induced by NADPH/ADP-Fe3+ in rat liver microsomes (Kamat & Devasagayam, 1996). Nicotinamide inhibited lipid peroxidation and protein oxidation (carbonylation) induced by the ascorbate–Fe2+ system in the rat brain mitochondria (Kamat & Devasagayam, 1999).

Nicotinamide exhibited a protective effect against UVA- and/or UVB-induced DNA damage in normal human epidermal melanocytes, as indicated by decreased levels of cyclobutane pyrimidine dimers and 8-hydroxy-2'-deoxyguanosine (Chhabra et al., 2019). Nicotinamide rescued the viability of a Chinese hamster ovary cell line (CHO AA8) irradiated with UV radiation and prevented apoptosis through mechanisms related to the stabilization of the cytoskeleton proteins, such as F-actin, vimentin, and beta-tubulin (Izdebska et al., 2018).

Nicotinamide attenuated the synthesis of inflammatory mediators, such as prostaglandin (PG) E2, IL-6, and IL-8 in human epidermal keratinocytes and in full-thickness three dimensional skin organotypic models that were stimulated by UV radiation (Bierman et al., 2020). Nicotinamide downregulated the expression of IL-6, IL-10, monocyte chemoattractant protein-1 and tumor necrosis factor (TNF)-alpha in UV-irradiated keratinocytes (Monfrecola et al., 2013).

Nicotinamide supplementation to human cells prolongs the replicative lifespan and retards the senescence (Matuoka et al., 2001; Lim et al., 2006). Matuoka et al. (2001) observed that nicotinamide reverses the aging phenotypes in human diploid fibroblasts as evaluated by cell morphology, senescence-associated beta galactosidase activity, and cell replication potential, and tentatively attributed this action of nicotinamide to the enhancement of histone acetyltransferase activity and subsequently altered gene expression.

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2.6 Thiamine Mononitrate

Thiamine Mononitrate, included as part of the essential vitamin mix in Kangen Ukon Sigma Softgels, is present at a concentration of 1 mg per 450 mg softgel. Thiamine Mononitrate is a derivative of thiamine, also known as vitamin B1. Thiamine Mononitrate is a more stable, non-hygroscopic, and less soluble form of thiamine (Vitamin B1), which makes it particularly suitable for use in health supplements. As a derivative, it retains the essential qualities of thiamine but offers advantages in terms of shelf life and ease of handling during the manufacturing process. Once ingested, Thiamine Mononitrate is converted into the active form of vitamin B1, which the body can utilize for various essential functions.

Vitamin B1 is an essential nutrient that plays a crucial role in converting carbohydrates into energy in the body. It is water-soluble, meaning it dissolves in water and is not stored in the body in significant amounts, so it needs to be consumed regularly through diet or supplements. Thiamine Mononitrate is commonly used in food fortification and supplementation. Additionally, Thiamine Mononitrate is sometimes included in multivitamin supplements to ensure adequate intake of vitamin B1.

A study demonstrated that vitamin B1 decreases the oxidative stress and the production of the reactive oxygen species (ROS), and also upregulates the production of the endothelial nitric oxide synthase enzyme to enhance the generation and bioavailability of nitric oxide (NO) and subsequently improves the integrity of vascular endothelium and prevent experimental vascular endothelial dysfunction (Verma et al., 2010). This study shown that vitamin B1 has several beneficial effects on blood vessels.

Vitamin B1 addition also increases the oxidation of pyruvate to acetyl-CoA, thus counteracting the accumulation of pyruvate and lactate in the cytoplasm (Mk & Kreisler, 1949). Excess accumulation of these metabolites due to thiamine deficiency may increase hypoxia-inducible factor-1 α (HIF-1α) thus worsening diabetic retinopathy (Zera and Zastre, 2018). A few pilot studies in humans reported beneficial effects of

vitamin B1 administration on diabetic nephropathy. Type 2 diabetic patients with early stage nephropathy experienced reduction of urinary albumin excretion after 3 months of vitamin B1 supplementation (Rabbani et al., 2009). It means that patients with type 2 diabetes who also had an early form of kidney disease (called nephropathy) saw a decrease in the amount of protein (specifically albumin) in their urine after they took vitamin B1 supplements for 3 months. This is important because having protein in the urine can be a sign of kidney damage, so a reduction is a good sign that the kidneys are healthier. The study by Rabbani and colleagues in 2009 suggested that vitamin B1 could be helpful for diabetic patients in protecting their kidneys.

Administration of thiamine or a derivative can influence carbohydrate metabolism by reducing metabolism through the alternate pathways of metabolism and improving metabolism via the pentose phosphate pathway. This has been demonstrated in diabetic animal models where treatment with thiamine reduced fasting glucose and HbA1 c levels (Thornalley et al., 2010).

It has been demonstrated that vitamin B1 prevents cell damage and apoptosis induced by high glucose in retinal microvascular cells (Beltramo et al., 2008; La Selva et al., 1996; Berrone et al., 2006; Beltramo et al., 2009; Beltramo et al., 2020), and reduces glycation of basement membrane proteins, potentially preventing the detachment of pericytes from retinal capillary wall (Beltramo et al., 2002; Beltramo et al., 2009).

Routine administration of vitamin B1 might improve endothelial function and therefore slow the development and progression of atherosclerosis, especially in patients suffering from impaired glucose tolerance and non-insulin dependent diabetes mellitus who are prone to develop accelerated atherosclerosis (Arora et al., 2006). Additionally, deficiency of vitamin B1 was observed to be associated with dysfunction of beta-cells and impaired glucose tolerance (Thornalley, 2005). Vitamin B1 deficiency leads to a marked impairment in insulin synthesis and secretion (Debski et al., 2011).

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2.7 Ascorbic Acid

Ascorbic Acid is included as part of the essential vitamin mix in Kangen Ukon Sigma Softgels, with a concentration of 1 mg per 450 mg softgel. Ascorbic Acid commonly known as Vitamin C, is a water-soluble vitamin that is essential for human health. It is perhaps one of the most well-known and studied vitamins, renowned for its numerous physiological functions and health benefits. Dietary sources of Ascorbic Acid include citrus fruits, berries, kiwi, papaya, bell peppers, broccoli, and leafy green vegetables. Incorporating Ascorbic Acid-rich foods into our diet or taking supplements as needed due to specific health conditions or dietary restrictions can help to ensure we maintain optimal levels of this essential nutrient for overall health and well-being.

Ascorbic Acid has been suggested as a therapy for several cancers through causing oxidative stress in cancer cells or boosting the effectiveness of specific chemical therapies (Lu et al., 2018). Ascorbic Acid seems to enhance chemo-sensitivity and is also helpful in reducing the toxicity of chemotherapeutic drugs in many types of cancer cells (Lee et al., 2017). It can prevent cancer by reducing oxidative DNA degradation, such as DNA mutations (Peng et al., 2022). Ascorbic Acid can also effectively provide electrons to Fe^{3+} to regenerate Fe^{2+}. This could trigger ferroptosis by increasing ferrous iron levels in colorectal cancer cells and promote the lethal metabolic cell death program induced by ATP depletion and oxidative stress (Ali et al., 2024).

Additionally, it has been suggested that Ascorbic Acid might encourage myelin growth in Schwann cells. This is particularly important in conditions where nerve damage has occurred, as enhancing myelin growth could potentially improve nerve function. Further, Ascorbic Acid functions as a co-factor in the synthesis of neurotransmitters, notably dopamine and norepinephrine, which are catecholamines (Kocot et al., 2017). Our immunological, neuron, and bone cells, in particular, require a lot of Ascorbic Acid to function at their best. It plays a role in synthesizing neurotransmitters, neuropeptides, carnitine, collagen, and other substances essential for wound healing, energy metabolism, and nervous system function (Vollbracht et al., 2011).

Ascorbic Acid exerts multiple effects on the viability and metabolism of human immune cells (Kogut et al., 2020). Ascorbic Acid has a number of properties that contribute to its immune-modulating effects (Wong et al., 2020). Besides, Ascorbic Acid is an antioxidant, based on its ability to donate electrons to molecules, it inhibits the oxidation of proteins, lipids, carbohydrates, and nucleic acids (Ströhle & Hahn, 2009) due to smoking habits (Traber & Stevens, 2011), chemical agents, endocrine disruptors (Heitzer et al., 1996), drugs (Aydo˘gan et al., 2008), and toxins. It is also a cofactor for mono- and dioxygenase, which stabilize collagen fibers, which in turn provide an optimal microenvironment for immune cells (Smithard & Langman et al., 1997).

Notably, patients with an infection suffer from Ascorbic Acid depletion that is proportional to disease severity (Lozano-Sepulveda et al., 2015). Therefore, it is not surprising that Ascorbic Acid seems to exert a protective role in acute and chronic viral infectious diseases (Carr, 2020). As regards acute viral infectious diseases, Ascorbic Acid has long been known to prevent and strengthen the response to acute viral infections ranging from common colds to more severe illnesses (Lee et al., 2014), in particular, it may exert protection against sepsis-induced acute respiratory distress syndrome and viral pneumonia (Carr, 2020; Adams et al., 2020).

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2.8 Folic Acid

Folic Acid is included as part of the essential vitamin mix in Kangen Ukon Sigma Softgels, with a concentration of 0.03 mg per 450 mg softgel. Folic Acid, also known as folate or Vitamin B9, is a water-soluble B-vitamin that plays a crucial role in various bodily functions, particularly in cell division and DNA synthesis. It is an essential nutrient required for the proper growth and development of the body. Folic Acid is found naturally in plants, such as the dark green leafy vegetables. Folic Acid is not synthesized de novo by humans, therefore the daily requirements are met from the dietary intake of Folic Acid supplements or food rich in this vitamin (Liew, 2016).

Folic Acid undergoes transformations in the body to become its active form, 5-methyltetrahydrofolate (5-MTHF), crucial for processes like red blood cell formation and fetal nervous system development. It is also associated with other forms like dihydrofolate (DHF) and tetrahydrofolate (THF) involved in the folate cycle, essential for transferring single-carbon units necessary for nucleotide biosynthesis, crucial for DNA building (Li et al., 2016). Adequate Folic Acid intake, either through diet or supplements, is vital for maintaining these physiological processes (Liew, 2016).

In metabolism, the physiological variants of Folic Acid that act as cofactors for enzymes are known as tetrahydrofolates (THF) and dihydrofolate (DHF). This process is essential for moving single-carbon groups necessary for the creation of nucleotides, the essential components of DNA (Field & Stover, 2017).

Folic Acid has been a component of multivitamin products and children's foods for more than 50 years, and it has shown no signs of being harmful as long as the consumption does not exceed the upper limit (UL) (Field & Stover, 2017).

Moreover, Folic Acid has been shown to improve endothelial function and reduce hypertension, especially in populations with low baseline folate levels. In patients with type 2 diabetes, Folic Acid supplementation can improve endothelial function and

glycemic control. There is also evidence that Folic Acid can reduce blood arsenic levels by enhancing arsenic methylation, which is particularly beneficial for populations exposed to high levels of arsenic (Gamble et al., 2007).

A substantial amount of research has shown that taking Folic Acid during pregnancy is effective in reducing the risk of birth defects. Folic acid, a pivotal nutrient in prenatal care, offers extensive benefits for pregnancy beyond its critical role in preventing neural tube defects. It supports the complex process of fetal development and maternal health, contributing to DNA replication and cell growth. The active form of this vitamin, once processed in the body, may also play a role in reducing other pregnancy-related risks. Recognized as an essential supplement for women of childbearing age, folic acid's comprehensive advantages underscore its recommendation as a standard part of prenatal nutrition, highlighting the need for further research into its broader implications for maternal and fetal well-being (Greenberg et al., 2007).

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2.9 Cyanocobalamin

Cyanocobalamin is included as part of the essential vitamin mix in Kangen Ukon Sigma Softgels, with a concentration of 0.01 mg per 450 mg softgel. Cyanocobalamin is a derivative of Vitamin B12, also known as cobalamin, a water-soluble vitamin essential for various physiological processes in the body. Cyanocobalamin is the most stable form of vitamin B12 and is commonly used in dietary supplements and pharmaceutical preparations due to its shelf stability (Greibe et al., 2017). In the body, cyanocobalamin is converted into the active forms of vitamin B12.

Vitamin B12 is unique among vitamins as it contains cobalt in its molecular structure. Cyanocobalamin, categorized chemically as a corrinoid, denotes a cobalt complex capable of crystallization. Its nomenclature, "cyanocobalamin" stems from the incorporation of a cyanide group into its structure. Approved by the United States Food and Drug Administration (FDA), cyanocobalamin finds application in treating pernicious anemia, malabsorption, atrophic gastritis and gastrectomy (Jägerstad & Arkbåge, 2003).

Cyanocobalamin is essential for preserving neurological health and aiding in the creation of red blood cells. It is crucial for the synthesis of DNA, which ensures cell division and proper cellular function (O'Leary & Samman, 2010). Research conducted between 2010 and 2018 indicates that taking 1000 µg of vitamin B12 orally is successful in restoring normal levels of B12 in the blood and reducing symptoms of deficiency. This method offers a less invasive and more cost-effective alternative to intramuscular injections (Andrès et al., 2018).

Furthermore, cyanocobalamin supports nerve cell health and the synthesis of fatty acids needed for the myelin sheath. This sheath insulates nerve fibers, improving the transmission of nerve signals (Calderón-Ospina & Nava-Mesa, 2019). Cyanocobalamin is easily absorbed from the gut into the bloodstream, making it an effective option for treating vitamin B12 deficiency.

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3.0 CONCLUSION

Kangen Ukon Sigma Softgels is formulated with a blend of 9 active ingredients, each ingredient has been the subject of extensive research, highlighting its role in health promotion. For instance, Turmeric Powder, the main ingredient, is renowned for its antioxidant and anti-inflammatory effects, potentially beneficial for various neurological disorders and chronic diseases. Squalene, another key component, is recognized for its antioxidant capabilities and potential anti-cancer properties. Fish Oil, rich in omega-3 fatty acids, is included for its cardiovascular benefits and anti-inflammatory effects.

The softgels also contain a spectrum of essential vitamins such as Riboflavin (Vitamin B2), Niacinamide (Vitamin B3), Thiamine Mononitrate (Vitamin B1), Ascorbic Acid (Vitamin C), Folic Acid (Vitamin B9), and Cyanocobalamin (Vitamin B12), each playing a vital role in maintaining overall health. Riboflavin aids in metabolism and cellular function, while Niacinamide supports skin health and inflammation regulation. Thiamine Mononitrate is crucial for energy production, Ascorbic Acid acts as an antioxidant, Folic Acid is essential for cell division and DNA synthesis, and Cyanocobalamin is vital for neurological health and red blood cell formation. Together, these ingredients make Kangen Ukon Sigma Softgels a potent supplement for enhancing well-being and managing health conditions.

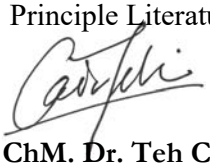
This literature review substantiates the efficacy of Kangen Ukon Sigma Softgels by highlighting the scientifically-backed benefits of each ingredient. Conducting literature reviews on active ingredients play a pivotal role in substantiating the health claims of Kangen Ukon Sigma Softgels. By analyzing previous research, literature reviews offer a broader context for understanding the effects of active ingredients and compiling comprehensive safety profiles.

Kindly be advised that the literature review report on the active ingredients of Kangen Ukon Sigma Softgels has been compiled from scientific journals and data from clinical

trials accessible online. It is important to note that no independent clinical trials have been conducted on the finished product itself to verify its efficacy. Therefore, the health benefits of the active ingredients cited in the report are intended solely for informational purposes and should not be construed as professional medical advice.

Dated: 25/6/2024

Principle Literature Review Author



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