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EFFECTS OF COMPOSITION AND PREPARATION CONDITION OF FORTIFIED MILK ON ABSORPTION AND BIOAVAILABILITY OF CALCIUM IN RATS

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EFFECTS OF COMPOSITION AND PREPARATION CONDITION OF FORTIFIED MILK ON ABSORPTION AND BIOAVAILABILITY OF CALCIUM IN RATS

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirements for the degree of Doctor of Philosophy

EFFECTS OF COMPOSITION AND PREPARATION CONDITION OF FORTIFIED MILK ON ABSORPTION AND BIOAVAILABILITY OF CALCIUM IN RATS

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December 2014

Chairman: **Mohd Yazid Abd Manap, PhD**
Faculty: **Food Science and Technology**

Calcium is an important mineral especially for the elderly. The average intake of calcium by the elderly women is below the reference nutrient intake (RNI). The amount of calcium absorption and calcium bioavailability in menopausal women is low. Therefore, the main aim of this research was to evaluate the effect of fortification and preparation condition on the absorption and bioavailability of calcium in milk powder formulas applied for ovariectomized (OVX) and OVX-osteoporosis (OS) rats. (1) skim milk powder (T1), (2) skim milk powder fortified with calcium carbonate (1300 mg), inulin (10 g), eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) (1.1 g), vitamins D_3 (10 µg), B_6 (1.5 mg) and K_1 (55 µg) (T2) and (3) skim milk fortified with calcium citrate (1300 mg), inulin (10 g), EPA + DHA (1.1g), vitamins D_3 (10 µg), B_6 (1.5 mg) and K_1 (55 µg) (T3) were formulated based on the North American and Western European dietary allowances. The ingredients were blended using high speed mixer for 5 minutes. The basal and fortified formulas were fed to OVX and OVX-OS rats and the plasma calcium, feces calcium, bone calcium content, bone breaking strength (maximum load), and bone morphology were measured to evaluate calcium absorption and bioavailability. The effect of particle size on absorption and bioavailability of calcium on OVX and OVX-OS rats was studied. Optimization on cycle and pressure of high-pressure homogenizer was done to produce T2-nano and T3-nano. *In vivo* study of calcium absorption and bioavailability in OVX and OVX-OS rats demonstrated that calcium fortification increased absorption and bioavailability. Calcium absorption and bioavailability showed a significant ($p < 0.05$) increase using T2 and T3 compared with T1 in OVX rats. Absorption and bioavailability of calcium from T2 were higher than T3 in OVX rats. The calcium absorption and bioavailability of T2-nano (absorption: 89.06% and bioavailability: 41.65%) and T3-nano (absorption: 80.22% and bioavailability: 34.82%) increased significantly ($p < 0.05$) compared with T2 (absorption: 63.54 % and bioavailability: 24.64%) and T3 (absorption: 33.66% and bioavailability: 15.94%) in OVX rats. T2-nano could enhance the calcium absorption and bioavailability better than T3-nano in OVX rats. The best milk powder for OVX rats was T2-nano with the positive effect of size reduction on absorption and bioavailability of calcium. It was observed that T2 and T3, in OVX-OS rats, had higher calcium absorption and bioavailability than T1. The calcium absorption and

bioavailability were improved with consumption of T2 compared with T3 in OVX-OS rats. The results provided that absorption and bioavailability of calcium in OVX-OS rats increased with consumption of T2-nano (absorption: 82.09% and bioavailability: 30.17%) and T3-nano (absorption: 68.67% and bioavailability: 20.38%) compared with T2 (absorption: 60.54% and bioavailability: 9.74%) and T3 (absorption: 42.87% and bioavailability: 4.23%). T2-nano in OVX-OS rats had more positive effect on absorption and bioavailability of calcium than T3-nano. The best milk powder for OVX-OS rats was T2-nano with the positive effect of size reduction on calcium absorption and bioavailability. The current study revealed that OVX rats exhibited higher calcium bioavailability and absorption than OVX-OS rats. In conclusion, this study had successfully developed as a safe and effective fortified milk powder because the basal diet and compounds composed of fully natural food grade components eligible for food application. They were added under limited dosage. The formula could increase calcium absorption and bioavailability and decrease bone loss in OVX and OVX-OS rats as a model of menopause and menopause-OS women.

Abstrak tesis yang dikemukakan kepadaSenat Universiti Putra Malaysia sebagai memenuhi keperluan untuki jazah Doktor Falsafah

KESAN KOMPOSISI DAN KONDISI PENYEDIAAN SUSU DIPERKAYA KE ATAS PENYERAPAN DAN KEBOLEHGUNAAN KALSIUM TERHADAP TIKUS

Oleh

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Kalsium adalah mineral penting kepada orang dewasa. Purata pengambilan kasium oleh wanita dewasa adalah dibawah paras pengambilan diet yang disarankan. Amaun kalsium yang diserap dan yang dapat digunakan oleh badan oleh OVX dan tikus OVX-OS. Olehitu, tujuan utama penyelidikan ini adalah untuk menilai kesan penambahan dan keadaan penyediaan keatas penyerapan dan kebolehgunaan kalsium didalam formulasi susu tepung spesifik untuk wanita menaposa. Susu tepung skim (T1, Formulasi asas), susu tepung skim yang ditambah dengan kalsium karbonat (1300 mg), inulin (10 g), EPA + DHA (1.1 g), vitamin D_3 (10 ug), B_6 (1.5 mg) dan K_1 (55 ug) (formulasi T2) dan susu skim yang ditambah dengan kalsium sitrat (1300 mg), inulin (10 mg), EPA + DHA (1.1 g), vitamins D_3 (10 ug), B_6 (1.5 mg) dan K_1 (55 ug) (formulasi T3) telah diformulasi mengikut saranan dari WHO-RNI untuk wanita menopaus. Bahan ini telah dicampurkan menggunakan pengisar berkelajuan tinggi selama 5 minit. Formulasi asas dan formulasi diperkaya telah diberikan kepada tikus OVX dan tikus OVX-OS. Kalsium plasma (mmol/l), kalsium tulang (%), kekuatan tulang pecah (N) dan struktur tulang telah diukur untuk menilai penyerapan kalsium (%) dan kebolehgunaan kalsium (%). Kesan saiz partikel keatas penyerapan dan kebolehgunaan kalsium oleh tikus OVX dan tikus OVX-OS telah dikaji. Pengoptimuman kitaran (kali) dan tekanan (bar) homogenizer tekanan tinggi telah dilakukan untuk menghasilkan formulasi T2-nano dan T3-nano. Kajian *in vivo* keatas penyerapan dan kebolehgunaan oleh tikus OVX dan tikus OVX-OS menunjukkan bahawa formulasi diperkaya kalsium meningkatkan penyerapan dan kebolehgunaan kalsium. Penyerapan dan kebolehgunaan kalsium menunjukkan peningkatan yang ketara pada tikus OVX yang diberi formulasi T2 dan T3 berbanding T1. Penyerapan dan kebolehgunaan kalsium oleh tikus OVX lebih tinggi bagi formulasi T2 berbanding T3. Penyerapan dan kebolehgunaan kalsium dari formulasi T2-nano dan T3-nano meningkat dengan ketara berbanding dengan T2 dan T3 oleh tikus OVX. T2-nano dapat meningkatkan penyerapan dan kebolehgunaan kalsium lebih dari T3-nano oleh tikus OVX. Olehitu, formulasi T2-nano untuk tikus OVX menunjukkan kesan positif untuk pengurangan saiz. Formulasi T2 dan T3 menunjukkan penyerapan dan keb oleh gunaan kalsium yang lebih tinggi oleh tikus OVX-OS berbanding dengan formulasi asas,T1. Peratus penyerapan dan kebolehgunaan kalsium meningkat dengan

pengambilan T2 berbanding dengan T3 oleh tikus OVX-OS. Keputusan ini menunjukkan bahawa penyerapan dan kebolehgunaan kalsium oleh tikus OVX-OS meningkat melalui pengambilan T2-nano dan T3-nano berbanding dengan pengambilan T2 dan T3.T2-nano memberikan kesan yanglebih positif keatas penyerapan dan kebolehgunaan kalsium oleh tikus OVX-OS. Olehitu, formulasi T2-nano member pengurangan saiz yang positif keatas tikus OVX-OS. Kajian terbaru ini menunjukkan bahawa penyerapan dan kebolehgunaan kalsium oleh tikus OVX adalah lebih tinggi berbanding oleh tikus OVX-OS. Rumusannya, kajian ini telah berjayamembangunkan formulasi susu tepung diperkaya yang selamat dan dapat meningkatkan penyerapan dan kebolehgunaan di dalam mengurangkan kehilangan jisim tulang oleh tikus OVX dan tikus OVX-OS sebagai model kepada wanita menaposa dan wanita menaposa-OS.

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I certify that a Thesis Examination Committee has met on 3 December 2014 to conduct the final examination of Arezoo Erfanian on her thesis entitled "Effects of Composition and Preparation Condition of Fortified Milk on Absorption and Bioavailability of Calcium in Rats" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirements for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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This is to confirm that:

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%	Percentage
<	Less than
>	More than
°C	Celsius degree
µg	Microgram
µL	Microliter
µm	Micrometer
AAS	Atomic absorption spectrophotometry
ACUC	Animal Care and Use Committee
AI	Adequate intake
ANOVA	Analysis of variance
APS	Average particle size
BMC	Bone mineral content
BMD	Bone mineral density
CCD	Central composite design
CH_3CN	Acetonitrile
CH_3OH	Methanol
CV	Coefficients of variation
d	Day
DHA	Docosahexaenoic acid
DI	Deionized
DV	Dependent variable
EAR	Estimated average requirement
ECF	Extracellular fluid
EFTEM	Energy filtered transmission electron microscopy
e.g.	For example
EPA	Eicosahexaenoic acid
et al.	And others
FA	Fatty acid
FAME	Fatty acid methyl esters
FAO	Food and agriculture organization
FRM	Final reduced model
g	Gram
GC	Gas chromatography
hrs	Hours
HCl	Hydrochloric acid
$HClO_4$	Perchloric acid
HPLC	High pressure liquid chromatography
HMF	Hydroxymethylfuraldehyde
i.e.	Meaning
I.S.	Internal standard
IV	Independent variable
kcal	Kilocalorie
kg	Kilogram
L	Liter
$LaCl_3$	Lanthanum oxide
LOD	Limit of detection
LOQ	Limit of quantification

m	Meter
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
MTBE	Methyl tert butyl ether
NDO	Non digestible oligosaccharide
ng	Nanogram
nm	Nanometer
NV	Normalized value
OC	Osteocalcin
OS	Osteoporosis
OVX	Ovariectomized
PDI	Polydispersity index
ppm	Parts per million
PUFA	Polyunsaturated fatty acid
RBV	Relative bioavailability value
RC	Regression coefficient
RE	Regression equation
RF	Response factor
RH	Relative humidity
RNI	Reference nutrient intake
rpm	Round per minute
RRF	Relative response factor
RRSM	Reduced response surface model
RSD	Relative standard deviation
RSE	Response surface equation
RSM	Response surface methodology
RV	Response variable
SCFAs	Short chain fatty acids
SD	Standard deviation
SEM	Standard error of the mean
S/N	Signal to noise
TEM	Transmission electron microscopy
TUIL	Tolerable upper intake level
UV	Ultraviolet
v/v	Volume per volume
WHO	World health organization
wt	Weight

CHAPTER I

INTRODUCTION

Osteoporosis is a skeletal disorder which ultimately increases the risk of bone fracture. It is one of the major health problems, and expected to increase dramatically in coming decades (National Osteoporosis Foundation, 2002). As recently reported, 1.66 million hip fractures occur each year worldwide. The incidence is predicted to increase fourfold by 2050 as the number of elderly people increases year by year (Van den *et al*., 2009). Calcium is one of the nutrients required for normal skeletal growth and mineralization. It plays an important role in regulating bone remodelling and bone mass (Matkovic *et al*., 1992). Calcium deficiency is a global public health problem, especially in developing countries (Ma *et al*., 2007). Untreated calcium deficiency can lead to severe consequences such as osteoporosis that is one of the major health problems worldwide (Hunt *et al*., 2007; Ma *et al*., 2007).

Osteoporosis, a skeletal disorder characterized by low bone strength, predisposes people to an increased risk of fracture (Finkelstein *et al*., 2006). It is increasing in the Western world and has been predicted to increase up to 300% until 2050 in Asia (Kruger *et al.,* 2003). It is a costly and debilitative disease affecting one in four women over the age of 50 and associated with significant morbidity and mortality (National Osteoporosis Foundation, 2002). Gradual loss of bone with aging is normal; however, it may be accelerated by factors such as menopause, serious health conditions or their treatment, and lifestyle factors such as inadequate diet, lack of exercise, smoking, or excessive alcohol consumption (WHO, 2004). The most common type of osteoporosis is menopausal bone loss associated with ovarian hormone deficiency, low calcium intake and bioavailability (Devine *et al*., 2004).

A sharp decrease in ovarian estrogen production is the predominant cause of rapid bone loss during the first decade after menopause (Campbell *et al*., 2001). Post-menopausal osteoporosis is a serious health problem in elderly women and is characterized by a decrease in bone mass, leading to fracture and imbalanced turnover of the bone (Tamaki *et al*., 1998); while the balance of bone formation and bone resorption is kept in the young, bone resorption exceeds bone formation due to various reasons such as menopause and ageing. In particular, the bone mass of many women after menopause decreases and the risk of fracture increases rapidly (Kanis *et al*., 1991). However, it is a disease that can be prevented by taking adequate nutrition (Grashoff, 2002; Scholz-Ahrens *et al*., 2004).

There are some solutions to this problem. For instance; increased calcium intakes can be a key way to solve this problem. Calcium balance studies demonstrated that calcium requirements increase after menopause in women. This finding, coupled with an early epidemiological study associating increased hip fracture rates with low calcium intake, strongly suggested the significance of adequate calcium intake with regard to osteoporosis particularly in post-menopausal women (Murray, 1996). Indeed, there is widespread interest in assuring adequate calcium intake at critical stages in a woman's life. Dietary calcium is essential when considering calcium requirements of the elderly since the bioavailability of calcium declines with age. Previous study on post-menopausal women showed reduction in calcium absorption led to bone loss (Swaim *et* *al*., 2008). Normally, approximately 30% of calcium in the diet is absorbed by the body and deposited in the skeleton. Improved calcium absorption could have major preventive effects on the occurrence of bone fractures and osteoporosis in the body (Looker *et al*., 1997). Milk and dairy products are the most popular and trusted sources of calcium. They can be taken for a long time, and are important to human health.

Besides the calcium content of the diet, absorption of dietary calcium in intestine is also a critical factor in determining the availability of calcium for bone development and maintenance. Calcium absorption via the intestines is usually regarded as a synonym for bioavailability (Guéguen *et al*., 2000). Bioavailability of nutrient is the proportion of dietary nutrient absorbed and utilized by certain organs. This definition considers the achievement of the nutrient to a fluid (*e.g.* blood) bathing in the site of action. In addition, the fluid can assist the nutrient to reach the site of action.

The bioavailability of a mineral depends directly on the extent in which the mineral is absorbed and distributed to the site of action and depends inversely on the extent in which it is metabolized and excreted prior to arriving at the site of action (Zeyuan *et al*., 1998). Specifically, the bioavailability of calcium from foods is an important concern because calcium intake is quite low in our diet. Most of the calcium in food is chemically bonded to other dietary constituents, and must be released in a soluble form (Ayed *et al.,* 2006).

Another way is by increasing calcium bioavailability using suitable composition. Fortification is the practice of increasing the content of essential micronutrients such as vitamins and minerals, in food to improve the nutritional quality of the food supply and provide a public health benefit with minimal risk to health (WHO, 2006). Supplements and fortified foods not only show an improved absorbability, but also are alternative sources of calcium to traditional foods. Fortified foods, such as fortified milk, can be alternative sources for women who cannot consume adequate amount of dietary calcium daily (Heaney *et al*., 2006). However, such alternative sources need to be evaluated in respect of bioavailability. It is significant to emphasize that the intestinal absorption is not essentially a reflection of calcium bioavailability to the organism because calcium should be used for bone formation and mineralization (Ranhotra *et al*., 2000). Chemically, the calcium compound utilized to fortify the food affects calcium bioavailability (Ayed *et al.*, 2006).

In addition, it is necessary to develop food components that stimulate bone formation or suppress bone resorption like prebiotics. Moreover, it is believed that omega-3 poly unsaturated fatty acids (PUFAs) have protective effects on bone mineralization (Stransky *et al*., 2009). Vitamin D is also essential for the development and maintenance of bone as it plays a significant role in assisting calcium absorption from the diet, and is influential in ensuring the proper renewal and mineralization of bone tissue (International Osteoporosis Foundation, 2006). Furthermore, vitamin B_6 has effect on mineralization of bone (Stransky *et al*., 2009). Vitamin K, a less known nutrient, is also important for bone health. The role of Vitamin K is vital in the production of specific proteins, such as osteocalcin, required in formation of bone (Zittermann, 2007). It is accepted that adequate amounts of vitamins D_3, K_1, and B_6, inulin, DHA and EPA are key elements for healthy bone development, maintenance of bone density and bone strength, and prevention of osteoporosis. These combined effects are resistive against the development of osteoporosis, a disease characterized by the dwindling of bone mass due to loss of calcium which causes pain especially in post-menopausal women (Dickinson**,** 2002).

Fortification with micro calcium particles results in low absorption efficiency than nano calcium particles. Therefore, the dosage of calcium needs to be raised to enable the optimal amount of absorption; however, a high dosage is not advantageous to the elderly (Huang *et al*., 2009). Thus, the last and the most important key solution are to increase calcium absorption and bioavailability by reducing particle size (Park *et al*., 2007). Nanotechnology is expected to resolve this issue. At nano size range, the properties of formulations may differ substantially from bulk compounds of the same composition, mostly due to the increased specific surface area, which may lead to enhance calcium absorption and bioavailability.

It is important to understand the effects of dietary calcium deficiency as well as calcium supplementation on bone health. To improve the absorption and bioavailability of dietary calcium, especially in menopausal women, four types of fortified milk powder has been developed and compared *in vivo* by OVX and OVX-OS rats as a model of menopause and menopause-OS women. It was hypothesized that the fortified milk with specific composition will improve the absorption and bioavailability of calcium in OVX and OVX-OS rats.

The main goal of this research was to investigate the effects of composition and preparation condition on the absorption and bioavailability of calcium in fortified milk powder in OVX and OVX-OS rats. The following specific objectives were also considered accordingly:

- To formulate the fortified milk powders and do proximate analysis;
- To optimize the preparation condition of calcium carbonate and calcium citrate nano fortified milk powders; and
- To evaluate the absorption and bioavailability of calcium in OVX and OVX-OS rats fed with fortified milk powders.

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