



Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

Available online at www.ijpsdronline.com

Research Article

Quantitative and Qualitative Assessment of Marketed Nutraceuticals for Active Ingredients and Heavy Metals for Safety and Efficacy

Rohit Bansal, Anju Dhiman*

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001. Haryana. INDIA

ARTICLE INFO

Article history:

Received: 23 September, 2021

Revised: 22 December, 2021

Accepted: 30 December, 2021

Published: 30 January, 2022

Keywords:

Carotenoids,
Heavy metals,
HPLC,
ICP-MS,
Vitamins & Minerals.

DOI:

10.25004/IJPSDR.2022.140109

ABSTRACT

The global nutraceutical market is expanding fast, and people nowadays are inclined towards nutraceutical supplements for daily micronutrient needs and health benefits in some disease conditions. Hence, ensuring the safe and effective use of these supplements is the need of the hour. The current study is aimed at determining the accuracy and regulatory compliance of marketed nutraceutical formulations by quantifying the active nutraceutical ingredients and heavy metal content in these formulations using advanced analytical techniques. Total 12 marketed formulations were selected and analyzed in NABL (National Accreditation Board for Testing and Calibration Laboratories) accredited laboratory using High-performance liquid chromatography (HPLC) and inductively coupled plasma-mass-spectrometry (ICP-MS). The quantified values were compared with label-stated values and recommended values as per FSSAI. The quantified values in two lycopene samples varied significantly (-16 and +16%) from the label stated content and were found non-compliant with the regulatory recommendations. The measured intake values of calcium and vitamin D varied from 24 to 204% from the recommended daily allowances established by FSSAI. The quantified daily intake values varied from 4.2 to 58 mg and from 4 to 21.5 mg for lycopene and lutein, respectively. Heavy metal content determination resulted in two samples deviating from the tolerance limits of heavy metals for lead and arsenic. The mean values for lead and arsenic were found to be 2.482 ± 6.921 and 0.311 ± 0.655 ppm, respectively. The present study results provided vital information on the composition of marketed nutraceutical formulations. The regulatory agencies require stringent monitoring practices to ensure compliance with the existing regulatory guidelines to provide the consumer safe and effective nutraceutical products.

INTRODUCTION

Nowadays, nutraceuticals are gaining popularity in the healthcare system due to their risk mitigation potential in various disease conditions with a lesser likelihood of adverse effects. Nutraceuticals possess beneficial health effects and are considered to be natural in form as they are derived from botanical sources. Apart from food or part of food originating from plants or animals, nutraceutical compounds also include macronutrients such as proteins, minerals, and amino acids.

In recent years, researchers have shown in their studies favorable outcomes of different nutraceuticals in multiple disease conditions such as bone disorders,^[1-2] diabetes

management,^[3-4] neoplasm,^[5-6] cardiovascular^[7-8] and neurological diseases.^[9-10] Due to increasing consumer awareness about the beneficial effects of nutraceuticals, the global nutraceutical market is growing at an unprecedented rate and is expected to reach USD 722.49 billion by 2027.

Since nutraceuticals are derived from herbal sources and have been used for substantial lengths of time without major toxicities, there is a misconception that these products are completely safe. This may be true for some nutraceuticals; however, it cannot be ascertained for all such products. The adverse effects of nutraceuticals are reported not only due to nutraceutical ingredients but

*Corresponding Author: Anju Dhiman

Address: Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001. Haryana. INDIA

Email ✉: ad_mdu@rediffmail.com; dhiman_anju@yahoo.com

Tel: +91-8295951007

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2022 Rohit Bansal *et al.* This is an open access article distributed under the terms of the Creative Commons Attribution- NonCommercial-ShareAlike 4.0 International License which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

also due to contaminants in these products. Pesticides and heavy metals are considered the most dangerous among all contaminants. The adverse effects of these contaminants vary from mild skin rash to respiratory severe, neurological, and reproductive disorders.^[11] Heavy metals' toxicity includes liver disorder, immune function disorder, cancer, cardiovascular toxicity, neurological disorders, hepatic and renal dysfunction.^[11-12] Toxicities of nutraceutical ingredients include spontaneous bleeding after prolonged exposure of high dose Ginkgo biloba, increased risk of hypercalcemia due to the interaction of calcium and vitamin D supplements with digoxin/thiazide diuretics; carcinoma, hepatotoxicity, genotoxicity, and mutagenicity associated with St. John's wort (*Hypericum perforatum*), cinnamon and *Aloe vera*.^[11,13] Further, the response of nutraceuticals varies from individual to individual; hence, in order to gain maximum therapeutic benefit and to avoid any significant adverse effects, nutraceuticals must be consumed in recommended dosages set out by regulatory agencies; and should be free from /or within the tolerance limits of contaminants set out by the agencies.^[14] Regulatory authorities have laid down stringent guidelines on contaminants and their tolerable limits. It is therefore imperative that the manufacturers comply with these guidelines. The current study aims to quantify widely used active nutraceutical ingredients (vitamin D, calcium, lycopene, and lutein) in marketed formulations to check the accuracy of label claims; and analyze the content of heavy metals (lead, cadmium, arsenic, and mercury) in these formulations. The ascertained quantities of nutraceutical ingredients and contaminants were further studied for their compliance with the nutraceutical regulations.

MATERIALS AND METHOD

A total of 12 formulations from different manufacturers marketed in India were randomly selected for the current study. These formulations were purchased from online retail stores. These include four samples containing both vitamin D and calcium, four samples containing lycopene, and the remaining four samples containing lutein. Each sample was assigned with a unique laboratory reference number and sample number. Particulars of each sample were recorded, including the name of the product, the manufacturer, sample description (i.e., color of the tablet/capsule), batch number, manufacturing date, and expiry date. The samples were analyzed from a NABL (National Accreditation Board for Testing and Calibration Laboratories) accredited laboratory.

Sample Preparation

The tablets were crushed, and content from capsules was extracted to prepare the sample solutions in 2% nitric acid supra pure for heavy metal determination and in laboratory grade methanol for determination of

ingredients, i.e., vitamin D, lutein, and lycopene. The sample solution was prepared as per Indian Standard (IS) 4285 for determination of calcium.^[15]

Determination of Vitamin D, Lutein, Lycopene, and Calcium

High-performance liquid chromatography (HPLC) was employed to assay vitamin D, lycopene, and lutein,^[16] and volumetric determination was performed as per IS 4285 for calcium.

The analysis of vitamin D, lycopene, and lutein was carried out on an Infinity 1260 HPLC system (Agilent) using a C18 column (Zorbax, Agilent) and Diode-Array Detection (DAD) detector at detection wavelengths of 264 nm, 572 nm, and 550 nm, respectively.

The linearity to validate the method was established using respective standard solutions with concentrations ranging from 1 to 20 mg/L for vitamin D and 5 to 100 mg/L for lutein and lycopene.

Determination of Heavy Metals

An Agilent 7700 inductively coupled plasma mass spectrometry (ICP-MS) was employed for evaluating heavy metals.^[16] The linearity to validate the method was established using standard solutions with concentrations ranging from 0.5 to 100 µg/L.

Identification and quantification of ingredients and heavy metals were made using respective external standards.

Recommended Limits of Nutraceutical Ingredients and Maximum Tolerable Limits for Heavy Metals

Recommended daily allowances (RDA) of vitamins and minerals laid down by the Food Safety and Standards Authority of India (FSSAI) were followed. As per these recommendations, the RDA for calcium varies between population groups: 600 mg/day for children (1 to 9 years) and adults (>17 years); 500 mg/day for infants (< 1 year of age); 800 mg/day for adolescents (10 to 17 years) and 1200 mg/day for pregnant and lactating women. There is only one value of RDA set out for all population groups in case of vitamin D, i.e., 10 µg/day (400IU).^[17]

Lycopene and lutein are included in Schedule VI (Part B) list of nutraceutical ingredients as per FSSAI regulations on nutraceuticals;^[18] however, FSSAI has not established an RDA for lutein and lycopene.

Maximum permissible limit (in parts per million [ppm] by weight) for contaminants laid down by Food Safety and Standard Regulations (FSSR) were followed for heavy metal content analysis. The heavy metal limits for processed food products other than infant milk substitutes are: 1-ppm for mercury (as Hg), 10 ppm for lead (as Pb), 1.5 ppm for cadmium (as Cd), and 1.1 ppm for arsenic (as As).^[19] In order to estimate the variation between the different samples, a single imputation method was employed, considering some samples may have metal

content below the level of quantification (LoQ), i.e., 0.01. Values below LOQ by LoQ to have consistent approach are replaced by a constant value such as LoQ/2 or the LoQ itself in the single imputation method. Using the upper value, i.e., LoQ itself is considered the most conservative method.^[20] In the current study, the mean and standard deviation of the heavy metal contents in different samples was calculated using a single imputation method using values below LoQ as LoQ.

RESULTS

The physical examination revealed normal color and intact formulation (tablets/capsules). The values of vitamin D, calcium, lycopene, and lutein were determined as content per serving (tablet/capsule) and were compared with values stated on the product label (Table 1). The retention

time (Rt) ranges (in minutes) for different samples were noted as follows: 2.622 - 2.654 for lutein, 2.999 – 3.044 for lycopene, and 5.104 – 5.288 for vitamin D. The quantified values vary significantly from the label stated content in two lycopene samples (Table 1). The variation was noted as -16 and +16% in these samples.

The recommended daily serving value (the number of tablets/capsules) specified on the product label was multiplied with the quantified values of vitamin D and calcium to determine the actual daily amount that the end-user will consume following the product label recommended dose. These values were determined to check the variation from the daily intake values recommended by FSSAI. Although the sample product labels didn't specifically mention the intended population of use, the values were determined with respect to adult

Table 1: Difference between the quantified and stated value of the selected samples of nutraceutical products

Sample number	Ingredients	Stated value (per tablet/capsule)	Quantified value (per tablet/capsule)	Percentage difference
0014	Lycopene	10 mg	9.98 mg	-0.2
0015	Lycopene	5 mg	4.20 mg	-16
0016	Lycopene	25 mg	29.0 mg	+16
0017	Lycopene	30 mg	28.0 mg	-6.67
0018	Calcium elemental	100 mg	98.99 mg	-0.1
	Vitamin D (as D3)	8.33 µg	8.10 µg	-2.76
0019	Calcium elemental	200 mg	210.20 mg	+5.1
	Vitamin D (as D2)	5 µg	4.80 µg	-4
0020	Calcium elemental	250 mg	248.70 mg	-0.52
	Vitamin D (as D2)	10 µg	10.20 µg	+2
0021	Calcium elemental	400 mg	420.80 mg	+5.2
	Vitamin D (as D2)	2.5 µg	2.40 µg	-4
0022	Lutein	10 mg	9.50 mg	-5
0023	Lutein	20 mg	21.50 mg	+7.5
0024	Lutein	10 mg	10.50 mg	+5
0025	Lutein	2 mg	2.02 mg	+1

Table 2: Variation of quantified daily intake value from the RDA specified by FSSAI for vitamin D and calcium

Sample number	Maximum daily serving (as per label)	Quantified dose per tablet (mg/µg)	Actual daily intake (mg/µg)	Percent RDA*†
Calcium (mg):				
0018	Two tablets	98.99	197.98	33
0019	Two tablets	210.20	420.4	70
0020	Two tablets	248.70	497.4	83
0021	One tablet	420.80	420.8	70
Vitamin D (µg):				
0018	Two tablets	8.10	16.2	162
0019	Two tablets	4.80	9.6	96
0020	Two tablets	10.20	20.4	204
0021	One tablet	2.40	2.4	24

*variation from RDA as specified by FSSAI for an adult man or woman, i.e., 600 mg for calcium and 10 µg for vitamin D

†Rounded off to a nearest whole number



men or women, considering all the product labels either mentioned "not recommended" or "to exercise caution" during use in pregnancy/lactation or in children. Upon calculation, the calcium daily intake value did not even reach one RDA (as recommended by FSSAI) in any of the samples (variation from 33 to 83%). On the other hand, vitamin D value was exceeded by twice the RDA in one sample (variation from 24 to 204%) (Table 2).

The daily intake values of lycopene and lutein were calculated based on recommended daily dosage specified on the product labels. It was found that the daily intake values calculated for these samples vary from 4.2 to 58 mg for lycopene; and 4 to 21.5 mg for lutein (Table 3).

Heavy metal content in all the samples was determined and compared with the permissible limits as per FSSR. The values were found deviating the permissible limits in two samples for arsenic and lead. In one of the samples, the value of lead was found more than double the permissible limits (Table 4). The estimate of the mean and standard deviation using the single imputation method is shown in Table 5.

Table 3: Actual daily intake calculated from the quantified value of lutein and lycopene and product label information

Sample number	Maximum daily servings (as per label)	Actual daily intake value based on quantified values (mg)
<i>Lycopene</i>		
0014	One capsule	9.98
0015	One tablet	4.20
0016	Two tablets	58.0
0017	One capsule	28.0
<i>Lutein</i>		
0022	One tablet	9.50
0023	One tablet	21.50
0024	One capsule	10.50
0025	Two tablets	4.04

Table 4: Recommended and quantified values of heavy metal content (in ppm)

	PL*	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
Pb	10	0.44	0.36	1.84	0.93	0.027	0.65	ε	ε	0.51	24.4	0.18	0.43
As	1.1	1.958	ε	ε	ε	ε	ε	0.28	ε	ε	1.40	ε	ε
Cd	1.5	ε	ε	ε	ε	ε	ε	ε	ε	ε	ε	ε	ε
Hg	1.0	ε	ε	ε	ε	ε	ε	ε	ε	ε	ε	ε	ε

*PL- Permissible Limit (as per FSSR, 2011)

ε Below the limit of quantification (0.01)

Table 5: Estimates of the mean and standard deviation of heavy metal content using single imputation method

	Permissible limit (ppm)	Mean ± SD
Lead (Pb)	10	2.482 ± 6.921
Arsenic (As)	1.1	0.311 ± 0.655
Cadmium (Cd)	1.5	NA
Mercury (Hg)	1.0	NA

NA: Not applicable in case all values are below LoQ

LoQ: Limit of quantification; SD: Standard deviation

DISCUSSION

As per FSSAI,^[18] the tolerance limit for variation of quantified value from the label declared value of the nutritional ingredients is ten percent. FSSAI permits appropriate overages based on scientific rationale; however, these are specified only for vitamins and minerals.^[18] Since the variation of more than ten percent ($\pm 16\%$) was identified for lycopene in two samples and no overages have been specified for carotenoids, these two samples were found out of the tolerance limits set by FSSAI. Further, the intended population of use was not specified on all labels, which is an important parameter considering the RDA defined by FSSAI varies among different population groups.

Calcium and vitamin D are vital for the maintenance of bone health. The major portion of daily calcium and vitamin D requirement can be completed from dietary intake along with adequate sunlight exposure. However, due to changing food habits and lifestyle modifications with long indoor working hours, the deficiency of vitamin D and calcium is quite rampant in India^[21-22] and around the world.^[13] These deficiencies can lead to several clinical consequences, including low bone mass, osteoporosis, and increased risk of falls and fractures.^[22-24] Since there is vast awareness of calcium and vitamin D supplements, most people rely on these supplements to fulfill their daily need of vitamins and minerals. In the current study, the calcium and vitamin D levels were found way below the RDA in some of the samples. Hence, intake of these supplements can offer a false sense of satisfaction and, in turn, lead to clinical consequences of vitamin D and calcium deficit. On the other hand, in some of the samples, the vitamin D levels were found way higher than the RDA; hence, there is also a risk of vitamin toxicity. A review of the literature revealed reports of calcium and vitamin D toxicities from marketed supplements resulting in the development of hypercalcemia, neuropsychiatric, gastrointestinal, renal,

and cardiovascular complications.^[25-27]

The daily intake values specified on the sample labels were not in line with the RDA established by FSSAI. Although the percent RDA is mentioned on all the labels of calcium/vitamin D samples; the consumer is likely to follow the label recommended dosage and not the percent RDA considering the definition of RDA is not mentioned on the product labels, and most of the consumers are not aware of the RDA terminology. Moreover, nutraceutical products are not prescription products and, most of the time, taken over-the-counter by the consumers to fulfill their vitamin/mineral requirement. Hence, it is likely to result in non-fulfillment of required calcium/vitamin D demand of the consumers or can lead to their overdose.

FSSAI has already identified the issue regarding non-compliant RDA values. One of the root causes of this issue is the lack of proper scrutiny by licensing authorities when issuing the licenses to manufacturers. FSSAI is taking steps in directing state licensing authorities to strictly scrutinize the RDA while granting new licenses. The authorities have started reviewing the existing licenses and issuing notices to manufacturers to direct them to perform necessary modifications if non-compliance is identified.

Among different tested samples, a considerable variation in label recommended values was also noticed for lutein and lycopene. Since the nutraceuticals are not prescription-based products and considering the notable variability in bioavailability of carotenoids from individual to individual, there is large possibility of adverse clinical outcomes due to improper dosage of lutein and lycopene from these supplements. Studies have shown that more than 20 mg/day of supplemental intake of carotenoids may result in adverse outcomes, including increased risk of cancer and death, especially in smokers.^[27] In the current study, the manufacturer of one of the lutein formulations claimed: "Zero side effects" on the label. As the possibility of the adverse event cannot be completely ruled out with carotenoids, providing such claims can lead to a false sense of security to consumers and more likely to feel invulnerable to negative health consequences. FSSAI restricts any claims that can be misleading to the public in any way.^[28] Such claims can also be considered a covert promotion, which FSSAI again prohibits. During heavy metal testing, the mean value for lead and arsenic in the studied samples was noted as 2.482 ± 6.921 and 0.311 ± 0.655 ppm, respectively, as compared to the permissible limits of 10 and 1.1 ppm. The value for cadmium and mercury was below the LOQ in all studied samples. A deviation percentage of +27% and +78% for arsenic; and +144% for the lead was noted in two samples from the tolerance limits. Although the values of heavy metal were within the permissible limits in most of the samples, a large deviation noted even in a few samples (especially in the case of +144% for lead) can be dangerous to the consumer leading to severe ramifications.^[29]

The results of this study exhibited deviation of marketed nutraceutical products from the existing regulatory guidelines in content variation from label stated values, level of contaminants, and labeling information. The reason for this deviation cannot be ascertained as it can be due to manufacturing or raw material defect or could be due to improper handling & storage. However, this certainly points towards the need for stricter regulatory monitoring for enforcement of good manufacturing practices (GMP) along with increased surveillance or inspections to ensure safety and efficacy for the consumers. A well-regulated and high-quality product will also ensure better acceptance of Indian products in the global market.

REFERENCES

1. Chen LR, Wen YT, Kuo CL, Chen KH. Calcium and Vitamin D Supplementation on Bone Health: Current Evidence and Recommendations. *International Journal of Gerontology*. 2014;8:183-188. Available from: doi.org/10.1016/j.ijge.2014.06.001
2. Pandey MK, Gupta SC, Karelia D, Gilhooly PJ, Shakibaei M, Aggarwal BB. Dietary nutraceuticals as backbone for bone health. *Biotechnology Advances*. 2018;36:1633-1648. Available from: doi.org/10.1016/j.biotechadv.2018.03.014
3. Nimesh S, Ashwlayan VD. Nutraceuticals in the management of diabetes mellitus. *Pharmacy & Pharmacology International Journal*. 2018;6:114-120. Available from: doi.org/10.15406/ppij.2018.06.00166
4. Sharma R, Amin H, Prajapati PK. Plant kingdom Nutraceuticals for diabetes. *Journal of Ayurvedic & Herbal Medicine*. 2016;2:224-228. Available from: www.ayurvedjournal.com/JAHM_201626_07.pdf
5. Gupta SC, Sharma A, Mishra S, Awasthee N. Nutraceuticals in Veterinary Medicine. Springer, Cham, 2019, pp. 603-610. Available from: doi.org/10.1007/978-3-030-04624-8_41
6. Ranzato E, Martinotti S, Calabrese CM, Calabrese G. Role of Nutraceuticals in Cancer Therapy. *Journal of Food Research*. 2014;3:18-25. Available from: doi.org/10.5539/jfr.v3n4p18
7. Alves QL, Camargo SB, Silva DF. Role of nutraceuticals in the prevention and treatment of hypertension and cardiovascular diseases. *Journal of Hypertension and Management*. 2019;5:037. Available from: doi.org/10.23937/2474-3690/1510037
8. Nikhra V. Nutraceuticals for improving cardiovascular health and prognosis in cardiovascular disease. *EC Nutrition*. 2019;14:434-448. Available from: doi.org/10.13140/RG.2.2.33613.49124
9. Makkar R, Behl T, Bungau S, Zengin G, Mehta V, Kumar A et al. Nutraceuticals in Neurological Disorders. *International Journal of Molecular Sciences*. 2020;21:4424. Available from: doi.org/10.3390/ijms21124424
10. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New Concepts in Nutraceuticals as Alternative for Pharmaceuticals. *International Journal of Preventive Medicine*. 2014;5:1487-1499. Available from: www.ncbi.nlm.nih.gov/pmc/articles/pmc4336979/
11. Helal NA, Eassa HA, Amer AM, Eltokhy MA, Edafiogho I, Nounou MI. Nutraceuticals' Novel Formulations: The Good, the Bad, the Unknown and Patents Involved. *Recent Patents on Drug Delivery & Formulation*. 2019;13:105-156. Available from: doi.org/10.2174/1872211313666190503112040
12. Gil F, Hernández AF, Martín-Domingo MC. Toxic contaminants of nutraceuticals and food ingredients. In: *Nutraceuticals: Efficacy, Safety and Toxicity*. Academic Press, Boston, MA, 2016, pp. 1-13. Available from: scitechconnect.elsevier.com/wp-content/uploads/2016/03/Nutraceuticals-Chapter58-1.pdf
13. Sunyecz JA. The use of calcium and vitamin D in the management of osteoporosis. *Therapeutics and Clinical Risk Management*. 2008;4:827-836. Available from: doi.org/10.2147/tcrm.s3552



14. Das L, Bhaumik E, Raychaudhuri U, Chakraborty R. Role of nutraceuticals in human health. *Journal of Food Science & Technology*. 2012;49:173-183. Available from: doi.org/10.1007/s13197-011-0269-4
15. IS 4285. Indian Standards. Method for volumetric determination of calcium. 1967. [cited September 19, 2020]. Available from: archive.org/details/gov.in.is.4285.1967/page/n5/mode/2up
16. Longvah T, Ananthan R, Bhaskarachary K, Venkaiah K. Indian Food composition tables. Hyderabad, India, 2017. Available from: www.indiaenvironmentportal.org.in/files/file/IFCT%202017%20Book.pdf
17. Food Safety and Standards Authority of India (FSSAI). Recommended Dietary Allowance (RDA)-reg. FSSAI.Gov. [Online] 2019 [cited September 19, 2020]. Available from: www.fssai.gov.in/upload/advisories/2020/01/5e159e0a809bbLetter_RDA_08_01_2020.pdf
18. Food Safety and Standards Authority of India (FSSAI). Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Food and Novel Food) Regulations. FSSAI.Gov. [Online] 2016 [cited September 19, 2020]. Available from: www.fssai.gov.in/dam/jcr:c0b36c0c-ccc9-446d-ada6-5b164de27460/Gazette_Notification_Functional_Foods_06_01_2017.pdf
19. Food Safety and Standards (FSSR) Regulations. Contaminants, Toxins and Residues. FSSAI.Gov. [Online] 2011 [cited September 19, 2020]. Available from: jaivikbharat.fssai.gov.in/pdf/Compendium_Contaminants_Regulations.pdf
20. Abdulla NM, Adam B, Blair I, Oulhaj A. Heavy metal content of herbal health supplement products in Dubai – UAE: a cross-sectional study. *BMC Complementary and Alternative Medicine*. 2019;19:276. Available from: doi.org/10.1186/s12906-019-2693-3
21. Aparna P, Muthathal S, Nongkynrih B, Gupta SK. Vitamin D deficiency in India. *Journal of Family Medicine and Primary Care*. 2018;7:324-330. Available from: www.ncbi.nlm.nih.gov/pmc/articles/pmc6060930/
22. Harinarayan CV, Akhila H. Modern India and the Tale of Twin Nutrient Deficiency–Calcium and Vitamin D–Nutrition Trend Data 50 Years-Retrospect, Introspect, and Prospect. *Frontiers in Endocrinology*. 2019;10:493. Available from: doi.org/10.3389/fendo.2019.00493
23. Hazell TJ, DeGuire JR, Weiler HA. Vitamin D: An overview of its role in skeletal muscle physiology in children and adolescents. *Nutrition Reviews*. 2012;70:520-533. Available from: doi.org/10.1111/j.1753-4887.2012.00510.x
24. Holick MF, Chen TC. Vitamin D deficiency: A worldwide problem with health consequences. *The American Journal of Clinical Nutrition*. 2008;87:1080S-1086S. Available from: doi.org/10.1093/ajcn/87.4.1080S
25. Lim K, Thadhani R. Vitamin D toxicity. *Brazilian Journal of Nephrology*. 2020;42:238-244. Available from: doi.org/10.1590/2175-8239-JBN-2019-0192
26. Pray WS, Pray JJ. Calcium Supplements: Benefits and Risks. *US Pharmacist* [Online]. 2004 [cited September 20, 2020]. Available from: www.medscape.com/viewarticle/497826
27. Zeratsky K. What is vitamin D toxicity? Should I be worried about taking supplements? *Mayo clinic* [Online] 2020 [cited September 20, 2020]. Available from: www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/expert-answers/vitamin-d-toxicity/faq-20058108
28. Böhm V, Lietz G, Olmedilla-Alonso B, Phelan D, Reboul E, Bánati D et al. From carotenoid intake to carotenoid blood and tissue concentrations – implications for dietary intake recommendations. *Nutrition Reviews*. 2021;79:544-573. Available from: doi.org/10.1093/nutrit/nuaa008
29. FSSAI (Food Safety and Standards Authority of India) Food Safety and Standards (Packaging and labelling) Regulations. [Online] version III 27 Aug. 2020 [cited May 2021]. Available from: www.fssai.gov.in/upload/uploadfiles/files/Compendium_Packaging_Labelling_Regulations_27_08_2020.pdf.

HOW TO CITE THIS ARTICLE: Bansal R, Dhiman A. Quantitative and Qualitative Assessment of Marketed Nutraceuticals for Active Ingredients and Heavy Metals for Safety and Efficacy. *Int. J. Pharm. Sci. Drug Res.* 2022;14(1):62-67. DOI: 10.25004/IJPSDR.2022.140109