Quercus spp. extract as a promising preventive or therapeutic strategy for cancer: A systematic review

PAULA A. OLIVEIRA[1,2], BEATRIZ MEDEIROS-FONSECA[2], CARMEN VASCONCELOS-NÓBREGA[2,3], ANTONIETA ALVARADO[2,4], MARIA JOÃO PIRES[1,2], HELENA VALA[2,3], ANA I.R.N.A. BARROS[2] and ANA I. FAUSTINO-ROCHA[2,5,6]

[1]Department of Veterinary Sciences, School of Agrarian and Veterinary Sciences (ECAV), University of Trás-os-Montes and Alto Douro; [2]Centre for The Research and Technology of Agro-Environmental and Biological Sciences (CITAB), Inov4Agro, 5000-801 Vila Real; [3]Agrarian School of The Polytechnic Institute of Viseu (ESAV-IPV), 3504-510 Viseu; Departments of [4]Veterinary Medicine and [5]Zootechnics, School of Sciences and Technology (ECT), University of Évora; [6]Comprehensive Health Research Center (CHRC), 7004-554 Évora, Portugal

Received July 29, 2022; Accepted January 31, 2023

DOI: 10.3892/mmr.2023.13062

Abstract. Acorns have traditionally been used in the human diet and for the treatment of specific diseases. Therefore, the present study performed a systematic review of studies which investigated the effects of *Quercus* spp. extracts in cancer prevention and treatment. A systematic literature search was performed for original records which addressed the anticancer effects of *Quercus* spp. extract in *in vitro* and *in vivo* cancer models. Body composition, food consumption, tumor development and/or toxicity were evaluated in *in vivo* studies, while cytotoxicity was evaluated in *in vitro* studies. Few studies and low sample sizes presented a challenge in the drawing of solid conclusions. Overall, the results suggested a positive impact of *Quercus* spp. extract, by reducing cancer development. Therefore, more studies with different cancer cell lines and animal models to address the efficacy of the acorn extracts in several types of cancer are required. Furthermore, the effects of acorn flour, incorporated in the diet, in an animal model of mammary cancer should be evaluated.

Introduction

Cancer is a leading cause of death worldwide, accounting for approximately 10 million deaths in 2020 (1). Breast, lung, colorectal, prostate, skin (non-melanoma) and stomach are among the most frequent types of cancer worldwide (1). The increasing number of cancer cases and deaths annually, the inefficacy of the strategies to prevent this disease and the adverse effects of the therapeutic approaches, have led an increasing number of studies to search for alternative and more effective approaches (1). According to the World Health Organization, strategies to reduce cancer risk include not using tobacco, maintaining a healthy body weight, eating a healthy diet (with fruits and vegetables), doing physical exercise regularly, avoiding harmful use of alcohol, minimizing exposure to ionizing radiation and reducing exposure to air pollution (1).

Plants have been used by humans since primitive times for food and medicines (2). Due to the presumable adverse effects of synthetic food additives on human health, in some cases resulting from antagonist synergies between the different synthetic compounds, and the increased consumer perception of this problem, there is a growing interest in obtaining natural extracts from human diet compounds (3).

Species of the genus *Quercus* spp., also known as oak, are a group of deciduous and evergreen trees of the family Fagaceae, which comprises around 600 species worldwide. They are widely distributed in temperate forests of the northern hemisphere and tropical climatic areas (4-6). These species may be found in the basin Mediterranean (Algeria, France, Italy, Morocco, Portugal, Spain and Tunisia), Asia, and North America (7). These trees, abundant in Southern Europe and in the Alentejo region in Portugal, are the basis of the sustainable agriculture system called 'Montado' (Portugal) or 'Dehesa' (Spain), a traditional silvo-pastoral land use system characterized by low density trees combined with agriculture or pastoral activities (8). Portuguese oak (*Quercus faginea*), holm oak (*Quercus ilex* or *Quercus rotundifolia*) and cork oak (*Quercus suber*) are the most common members of the Fagaceae family in Portugal (9). Almost all parts of the plants of the genus *Quercus* spp., including fruit, bark and leaves, display numerous medicinal properties. Therefore, they have been used in folk medicine in numerous countries and by numerous tribes to treat conditions, including asthma, colitis, diarrhea, furuncles, gonorrhea, hemorrhoids, labor pains, mucosa inflammation, obesity and stomatitis (10-13).

Correspondence to: Professor Ana I. Faustino-Rocha, Department of Zootechnics, School of Sciences and Technology (ECT), University of Évora, Herdade da Mitra, 7004-554 Évora, Portugal
E-mail: anafaustino.faustino@sapo.pt

Key words: acorn, extract, *in vitro*, *in vivo*, oak, oncology, *Quercus* spp.

Acorn is a fruit of the trees of the genus *Quercus* spp. It is nutritionally considered a rich product, with a higher nutritional value than cereals (14-17). The acorn is an excellent source of minerals (calcium, magnesium, phosphorus and potassium), unsaturated fatty acids (oleic acid) and essential fatty acids (linoleic and linolenic acids) (18-20). Starch is the largest nutrient component of acorns (about 55%) (21). Moreover, acorns contain numerous biologically active compounds such as flavonoids, phenolic acids, and tannins, which are important in the human diet to maintain an adequate level of antioxidants (4,6,22-29) and consequently to prevent certain diseases, such as heart diseases, diabetes and cancer. The acorn was used as a food stuff in the Mesolithic era and constitutes more than half of the diet of native people in the North American West Coast (30-36). In the northeast of the Iberian Peninsula, the acorn was used raw, boiled, roasted and like coffee, and used to make oil, soup, mush/porridge, cake, bread and coffee-like beverages (30-36). The oil obtained from the acorn is a nutritious cooking oil similar to oils obtained from avocado, cotton, olive and peanut (17).

The pharmacological effects of acorn include antioxidant, antimicrobial, anti-inflammatory, antidiabetic, hepatoprotective, anti-obesity, anticancer and anti-neurodegenerative effects, which has promoted its use on both food and medicine (3,37,38). Although it was an important ingredient in the past, it has been under-appreciated in modern times, and it is still far from being as widely used as other nuts. Acorn consumption declined over the last few centuries and it is now mostly associated with livestock feeding, to increase the nutritional value of meat and meat products (4,14,17). It should be noted that the high content of tannins is a problem that may limit the acorn consumption. These compounds belong to the group of polyphenols that cause bitterness and form complexes with proteins, polysaccharides and metal ions, reducing its digestibility and absorption (39,40). When they complex with salivary proteins the astringency caused can be very unpleasant, which may compromise its acceptance and consumption (21).

The Holm oak (*Quercus ilex*) produces the sweetest acorns when compared with other oak species due to a lower level of tannins; due to this, the Holm oak acorns are traditionally made into flour to mix with wheat and other cereals (9,41). This flour is a valuable source of macroelements (calcium, magnesium and potassium), microelements (copper, iron, manganese and zinc), vitamins from complex B, tocopherols, dietary fiber, unsaturated fatty acids (linoleic acid) and antioxidant substances (polyphenols) (22,42-46), improving the nutritional and sensorial characteristics of the final product within which it is used (47-51). Due to the absence of gluten proteins, this flour has recently been used for the production of gluten-free foods, adequate for people with gluten intolerance, such as patients with celiac disease (36,40,52,53). Furthermore, due to its unique characteristics, acorn flour can be considered an adjuvant for cancer prevention and therapy, adding value to the product (22).

An up-to-date assessment of the literature on the benefits of *Quercus spp*. extracts for cancer prevention and treatment might promote further research to validate its use. Therefore, the presented study performed a systematic review and meta-analysis of studies which had investigated the effects of *Quercus* spp. extracts in cancer prevention and treatment.

Materials and methods

Study protocol. The internationally accepted preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (54) were followed for all steps in the present study.

Data sources and search strategy. An electronic literature search was performed in four different databases [PubMed, Cochrane Library, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Web of Science and Science Direct] to identify studies which investigated the effects of *Quercus* spp. extract on cancer prevention or treatment. Keywords were searched by combining Medical Subject Headings with text terms related to cancer and oak as follows: 'quercus', 'acorn', 'oncology', 'cancer', 'disease', 'extract' and 'flour', in English, Portuguese and French. The terms were searched in these three languages and the papers were also reviewed in these languages. Previously published systematic reviews and references cited in the retrieved articles were also assessed to identify potentially eligible studies. Boolean operators (AND, OR) or its meta and truncation were used when appropriate to increase the number of relevant papers. The search results were exported to a Microsoft Excel sheet and duplicate papers were removed.

Study selection and inclusion criteria. The review included full text articles published in English, Portuguese or French. The articles were reviewed for inclusion through scanning of the titles and abstracts for relevance. Articles deemed important (i.e. articles with information concerning the effects of *Quercus* spp. extract in cancer using *in vitro* or *in vivo* approaches) or for which decisions were difficult to exclude were retained for full-text review. *In vitro* studies or *in vivo* randomized controlled trials with humans and animals with any kind of cancer were considered. It was confirmed that all studies were approved by the relevant Ethics Committee and that patient consent was obtained, when applicable. Studies with humans of any gender, race or ethnicity and all settings (i.e., local communities, nursing homes and hospitals) worldwide were considered. Similarly, studies with animals from any species, race/strain or gender were considered. All studies included a clarification of the exposure (i.e., dose, consumption duration and frequency) and evaluated at least one health outcome (i.e., body composition, tumor development or cytotoxicity). Conference abstracts, reviews, trial protocols, book chapters, studies without control group, case reports, and commentaries or opinions were excluded. There was no restriction based on the year of publication or sample size. The inclusion and exclusion criteria were summarized in Table I.

Data extraction. The studies were randomly distributed by the researchers. Each of them analyzed the papers and met to discuss them. All eligible studies were reviewed and each study was given an identifying code. Information on the sample (number of subjects or animals, age and/or cell line), exposure (oak species, dose, duration and frequency), groups (treated and control group) and outcomes (body condition, tumor development/size/volume and cytotoxicity) was extracted from the relevant studies.

Table I. Literature search strategy.

Parameter	Inclusion criteria	Exclusion criteria
Article type	Full text	Conference abstracts, reviews, trial protocols, book chapters, studies without control group, case reports, and commentaries or opinions
Language	English, Portuguese, French	
Study design	*In vitro* studies, *in vivo* randomized controlled trial, Ethics Committee approval and patient consent	
Sample	Humans from any gender, race or ethnicity and animals from any species, race/strain, or gender	
Exposure	*Quercus* spp., dose, consumption, duration and frequency	
Outcomes	Body composition, tumor development, cytotoxicity	

Risk of bias and study quality assessment. The risk of bias was assessed using the revised version of the Cochrane risk of bias tool (RoB 2.0), which consists of a fixed set of bias categories (55). A total of five specific categories were evaluated as 'high risk of bias', 'low risk of bias' or 'some concerns' to establish the overall risk of bias as follows: i) bias arising from the randomization process; ii) bias due to deviation from intended interventions; iii) bias due to missing outcome data; iv) bias in the measurement of the outcome; and v) bias in the selection of reported results. The researchers could also present personal judgment about the risk of bias in each category, which was reflected in the overall judgment value.

Statistical analysis. All outcomes were meta-analyzed, using Comprehensive Meta-Analysis (CMA; version 2) software (https://www.meta-analysis.com/), when at least two studies provided data. Outcomes, measured as the mean change from baseline to endpoint of the intervention study between the treatment and placebo groups, were considered continuous variables. $P<0.05$ was deemed to indicate a statistically significant difference.

Results

Study selection. The PRISMA flow diagram summarized the study selection process (Fig. 1). The search identified a total of 219 articles: 71 from Web of Science, 46 from Science Direct, 43 from LILACS and 59 from PubMed. After removing duplicates (n=28) and screening the remaining articles (n=191) by title and abstract, 185 were excluded as irrelevant. Of the six articles assessed by full-text review, two were excluded because they were not related to the exposure of interest. Finally, a total of four studies were included in the systematic review: three *in vitro* studies (56-58) and one mixed study with an *in vivo* and *in vitro* approach (59) (Table II). Assessment of the risk of bias, i.e. a critical analysis in which the strengths and the limitations of the studies were assessed, was performed in this review, and the risk was considered low.

Study characteristics and outcomes. A summary of the characteristics and outcomes of the studies included in this systematic review was presented in Table II. The studies were published between 2006 and 2017. In the *in vitro* studies breast, colorectal and glioblastoma cancer cell lines were used. The mixed (*in vitro* and *in vivo*) study, was published in 2015 and assessed the effects of oak infusion in 68 female Sprague-Dawley rats of five weeks of age (59). The MCF-7 human breast cancer cell line was used in both *in vitro* studies which evaluated the role of *Quercus* spp. extract in breast cancer (56,57). One of the studies used two cell lines in addition to the MCF-7 cell line, the Kpl-1 and Mfm-223 cell lines (56). The concentration of the extract as well as the time of exposure was different among *in vitro* studies. The concentrations ranged from 10 and 250 μg/ml, while the time of exposure ranged from 15 min to 48 h. A cytotoxic activity was reported in all *in vitro* studies, along with decreased protein levels of cyclooxygensase (COX)-2, interleukin (IL)-8 and IL-10, and inhibition of reactive oxygen species (ROS) in certain studies. In the *in vivo* study, the animals were exposed to the carcinogen 1,2-dimethylhydrazine to induce colorectal carcinogenesis and were provided with a 1% oral infusion of *Quercus sideroxyla*, *Quercus durifolia* or *Quercus eduardii*, for 26 weeks. The group treated with *Quercus sideroxyla* presented a lower mean number and multiplicity of colorectal tumors, and lower β-catenin protein level in adenocarcinomas, when compared with animals not treated with the infusion. Where qualitative data was obtained from <2 studies, meta-analysis was not performed.

Discussion

Cancer is a leading cause of death worldwide, and it is associated with several risk factors, including lifestyle (1). At

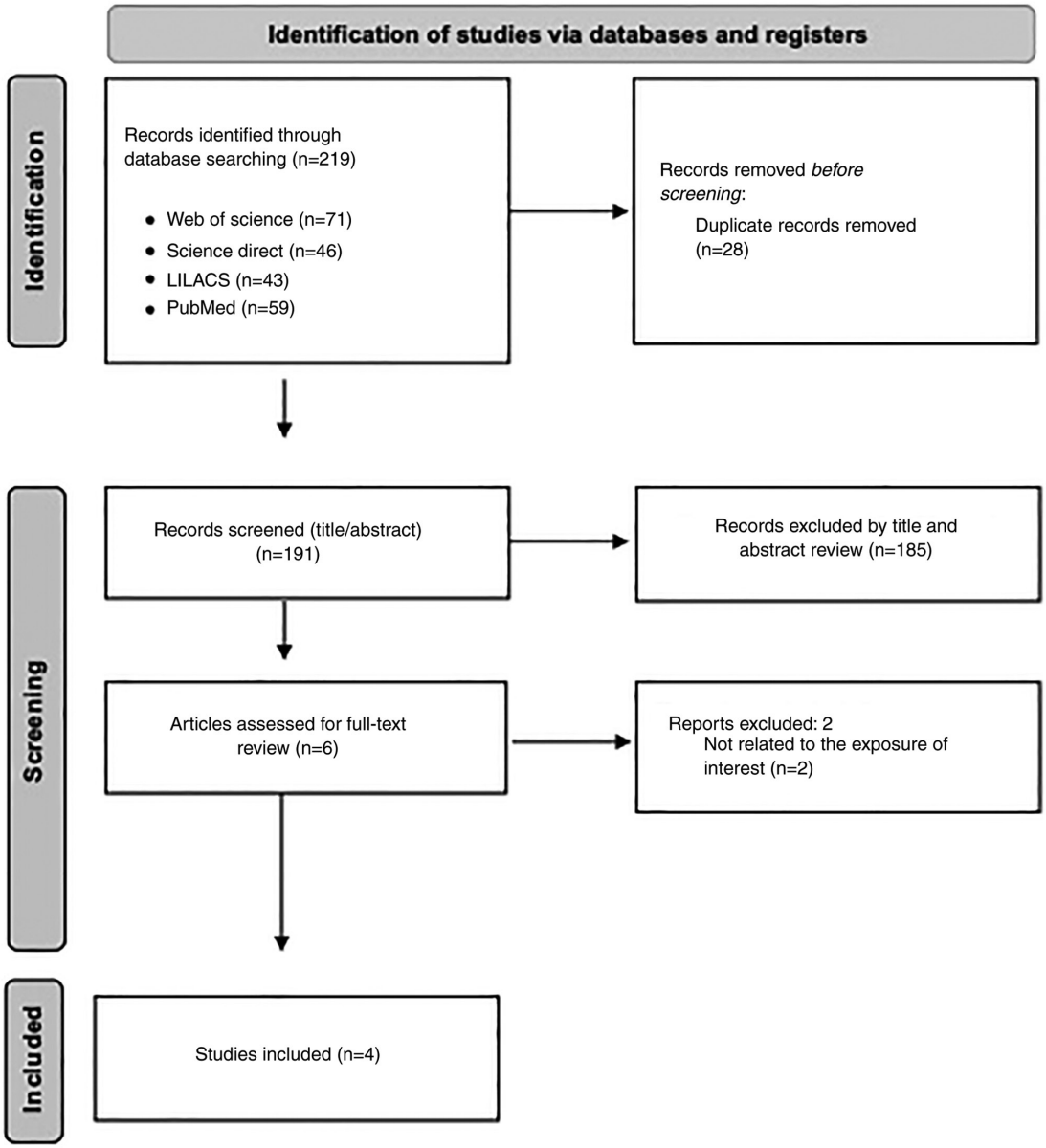

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flow diagram describing the selection process.

present, the human diet is changing. The Food and Agriculture Organization has underlined the importance of re-designing food production systems based on the fundamentals of the circular economy, with the aim of upgrading the efficient use of resources, giving new use to underexploited properties (60). The current global food system must adapt to the expected growth of the world population to ~9 billion individuals by 2050 and the effects of climate changes. This adaptation will probably include an increased consumption of edible wild foods, due to their richness in micronutrients and bioactive compounds, besides providing a cost-effective and sustainable way of improving calorific food security (22). Moreover, epidemiological research has indicated that a regular ingestion of plant polyphenols increases protection against different types of cancer, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases (61,62). The present systematic review analyzed the effects of *Quercus* spp. extracts in cancer prevention and treatment.

The effects of *Quercus* spp. extract have been previously assessed in certain diseases beyond cancer, including diabetes mellitus, neurodegenerative diseases, allergic asthma, gastric ulcer, colitis, vaginitis, acne vulgaris and episiotomy wounds. Its antimicrobial effects along with antiangiogenic potential have also been assessed (Table SI).

The number of studies in the cancer field are limited, and only three *in vitro* studies and one mixed study involving *in vitro* and *in vivo* approach have been previously performed addressing the role of *Quercus* spp. extract in cancer development, to the best of our knowledge. These studies were included in the present review and the data was extracted accordingly. The findings demonstrated that *Quercus* spp. extract had positive effects in breast and colorectal cancer cell lines, reducing cell viability and decreasing protein levels of COX-2, IL-8, IL-10, as well as ROS. In the *in vivo* study, the *Quercus* spp. extract did not affect body weight or food consumption, and decreased the mean number and

Table II. Summary of the studies evaluating the effects of *Quercus* spp. extracts in cancer, included in the present meta-analysis.

ID	First authors, year	Issue	Cells/animals	Groups	Age	Species/compound	Dose/concentration	Duration	Outcomes	(Refs.)
1	Eggenschwiler *et al*, 2006	Breast cancer	Human breast cancer cell lines: MCF-7, Kpl-1 and Mfm-223	-	-	*Quercus* spp. extract	0.01-0.1 mg/ml	48 h	Proliferation reduction of 12% for MCF-7 cells, 63% for Kpl-1 and 70% for Mfm-223	(56)
2	Heydari and Rashidipour, 2015	Breast cancer	Human breast cancer MCF-7 cells	-	-	Extract of *Quercus ilex* acorns containing silver nanoparticles Silver nanoparticles	Silver nanoparticles: 10, 20, 30, 40 and 50 μg/ml Extract and silver nanoparticles: 0.02, 0.03, 0.04 and 0.05 μg/ml	24 h	The cytotoxic effects of nanoparticles increased in the presence of the extract	(57)
3	Moreno-Jimenez *et al*, 2015	Colorectal cancer	Human colorectal adenocarcinoma HT-29 cells	-	-	Lyophylized extract from *Quercus sideroxyla*, *Quercus durifolia*, and *Quercus eduardii*	0.050, 0.075, 0.100, 0.125 and 0.150 mg/ml	3 h	*Q. sideroxyla* decreased COX-2 and IL-8 expression *Q. eduardii* decreased TNFα expression *Q. durifolia* increased nuclear factor-κB and tumor necrosis factor α COX-2, IL-8 and IL-10 levels decreased in all treatments	(59)
			68 male Sprague-Dawley rats 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis	Control (n=6) DMH (n=17) DMH + *Q. sideroxyla* (n=15) DMH + *Q. durifolia* (n=15) DMH +	5 weeks	Oak infusion of *Quercussideroxyla*, *Quercus durifolia*, and *Quercus eduardii*	1% (w/v), oral infusion	26 weeks	Body weight and food consumption were similar among groups *Q. sideroxyla*-treated group had a lower mean number	

Table II. Continued..

ID	First authors, year	Issue	Cells/animals	Groups	Age	Species/compound	Dose/concentration	Duration	Outcomes	(Refs.)
				Q. eduardii (n=15)					and multiplicity, and β-catenin protein level in adenocarcinomas *Q. eduardii* and *Q. durifolia* had no protective effects	
4	Amessis-Ouchemoukh *et al*, 2017	Glioblastoma	Human glioblastoma U87 cells			Extract of holm oak acorns from *Quercus ilex* L.	25, 100 and 250 µg/ml	15 min 30 min 60 min	Reactive oxygen species inhibition and cell viability reduction in a concentration dependent manner	(58)

DMH, 1,2-dimethylhydrazine; COX, cyclooxygenase; IL, interleukin.

multiplicity of tumors, and the protein expression level of β-catenin in colorectal adenocarcinomas. Due to an insufficient number of studies focusing on the effects of *Quercus* spp. in cancer, a meta-analysis was not performed. Overall, direct comparison with other systematic reviews is challenging due to methodological variations. However, in line with the results of the present study, earlier reviews reported potential positive effects of *Quercus* spp. extract in cancer development.

Despite the frequent use of *Quercus* spp. in folk medicine since ancient times, the present analysis identified few studies which addressed the role of this plant in cancer treatment. To the best of our knowledge, the present study is the first systematic review to evaluate the effects of *Quercus* spp. extract on cancer development. This review was based on the best current standards for systematic reviews and meta-analysis. The Cochrane risk of bias tool was used for individual randomized controlled trials and the reporting of this review was based on the PRISMA statement. The multidisciplinary team was composed of relevant experts with a long experience in research, literature search and scientific writing.

There were certain limitations of the present systematic review. The literature search was limited to Portuguese, English and French language reports. Due to the limited number of studies within the inclusion criteria, meta-analysis was not performed. The authors of the included studies were not contacted for further details. However, the findings could still provide insights into the effects of *Quercus* spp. extract on cancer development and lead to the development of new studies in the field.

The findings of the present study suggested that *Quercus* spp. extract was safe and demonstrated positive effects on colorectal cancer development. Despite this, it should be noted that a small number of studies and low sample sizes posed a challenge in drawing solid conclusions. Therefore, more studies with different cancer cell lines and animal models, including chemically-induced models and xenograft models using cell lines evaluated *in vitro*, are required to assess the efficacy of the acorn extracts in numerous types of cancer. Furthermore, the effects of acorn flour, incorporated in the diet, in an animal model of chemically-induced mammary cancer should be evaluated in a future study.

Acknowledgments

Not applicable.

Funding

The present study was supported by National Funds by Portuguese Foundation for Science and Technology, under the project nos. UIDB/04033/2020 and LA/P/0126/2020, and the PhD grant no. 2020.07675.BD.

Availability of data and materials

The datasets used and/or produced during the current study are available from the corresponding author on reasonable request.

Authors' contributions

PAO, BMF, CVN, AA, MJP, HV, AIRNAB and AIFR performed the analysis of the papers, and were involved in the manuscript writing and data confirmation. AIFR was responsible for the study design and manuscript submission. AIFR and PAO confirmed the authenticity of all the raw data. All authors read and approved the version of the manuscript submitted.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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