INPLASY PROTOCOL

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None declared.

Application of the Extracts of Pomegranate in Oral Cancer

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Review question / Objective: **In this scoping review we will focus on identifying those studies that investigated the effects of Punica granatum extracts on oral cancer and more specifically on OSCCs, summarizing the main results and the state of the research at the present time.**
Eligibility criteria: **All studies investigating Punica granatum L. in association with oral and precancerous cancer were considered potentially admissible, no restrictions were applied in relation to the year of publication and based on the language provided that an abstract in English is available. literature reviews were excluded and were used only as sources for bibliographic research.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 September 2022 and was last updated on 07 September 2022 (registration number INPLASY202290027).

INTRODUCTION

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Background: **The Pomegranate (Punica granatum L.) (Figure 1)is an ancient fruit plant native to south-western Asia (Iran, Pakistan, Afghanistan) but by virtue of its wide adaptability to pedoclimatic conditions, the plant has been widely cultivated in the rest of the world; It belongs to the Litraceae family and of its genus we have only one other species, the Punica protopunica, there are about 500 cultivars in the world that differ in their morphological and nutritional characteristics; The fruit is rich in polyphenols whose extract is consumed as food and is considered safe.**

In medicine it is used for its antioxidant properties, it has a rich component of tannin polyphenols among which the most bioactive are: punicalagin (flavonoids) and anthocyanins (delphinidin, cyanidin, pelargonidin), which are mainly found in the skins and in the pericarp, but also in the arils, flowers and leaves (figure 2); This small tree is therefore rich in bioactive molecules with therapeutic activity.
However, all parts of Punica granatum have been used for therapeutic purposes: leaves, flowers, bark, roots, peel, juice, seeds; their uses find application as anti-inflammatory , analgesic in the management of postmenopausal symptoms being weakly estrogenic, but also in erectile dysfunction, in diabetes and cardio-vascular disease , in the treatment of arthritis in Alzheimer's disease ; it also has bactericidal , antifungal and antiviral properties , its use in chronic gingivitis has also been evaluated in the dental field .
Among the main oral cancer, we have oral squamous cell carcinoma (OSCC) which represents about 90% of total cases, histologically it consists of a multilayered epithelium consisting of squamous cells with the presence of cellular and nuclear atypia; clinically it can manifest itself as an ulcer (erythroplakia), or a white plaque (leukoplakia) sometimes ulcerated with poorly defined margins, the localization of which can affect the entire epithelium of the oral cavity. The annual incidence in the world is 350,000 new cases diagnosed, with a higher incidence in the population over 50 years of age.
5-year survival is less than 50% and the therapies used to cope with the cancer lead to a moderate reduction in the quality of life with difficulties in speaking, swallowing, feeding and with difficulties for patients in relational life.
The main recognized risk factors are smoking and alcohol with a synergistic effect, moreover, traumatic events can contribute to the pathogenesis of OSCC, along with genetic factors, ultraviolet radiation, immunosuppression and nutritional factors.

Rationale: Punica granatum extracts also show interesting anticancer activities in influencing tumorgenesis and angiogenesis and cell transformation and proliferation. Punica granatum was therefore tested for use in the prevention of many cancers .
Its ability to inhibit cell proliferation has been tested on many cancer cell lines such as breast, leukemia , prostate, lung and fibrosarcoma but its antitumor effect on oral cancer cell lines has not been adequately documented; there are only a few studies in the literature that have investigated the anticarcinogenic role of Punica granatum on the cell lines of squamous cell carcinoma.
The main recognized risk factors are smoking and alcohol with a synergistic effect, moreover, traumatic events can contribute to the pathogenesis of OSCC, along with genetic factors, ultraviolet radiation, immunosuppression and nutritional factors.
Precisely in order to be able to reduce the risk factors for OSCC through the use of compounds with high nutritional value, the research has turned its attention to traditional natural medicine and to the identification of foods that could contain bioactive principles towards precancerous and cancers; Punica granatum is therefore an ideal candidate for its high content of polyphenols, tannins and flavonoids.

METHODS

Strategy of data synthesis: The search was carried out on 3 databases (PubMed, Scopus, and Science Direct) and a register (Chocrane library), in addition, a gray literature search was performed on Google scholar and Opengray (DANS EASY Archive), potentially eligible articles were also searched among references from literature reviews on Punica granatum L.
The authors responsible for researching the studies used the following key words in the databases: punica granatum AND cancer. The key words used on PubMed are shown below; Search: punica granatum AND cancer("pomegranate"[MeSH Terms] OR "pomegranate"[All Fields] OR ("punica"[All Fields] AND "granatum"[All Fields]) OR "punica granatum"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR

"canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]). Translations, punica granatum: "pomegranate"[MeSH Terms] OR "pomegranate"[All Fields] OR ("punica"[All Fields] AND "granatum"[All Fields]) OR "punica granatum"[All Fields] cancer: "cancer's"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]e research was conducted between 1 august 2022 and 15 august 2022 with a last update of the records identified on 19 august 2022.

Eligibility criteria: All studies investigating Punica granatum L. in association with oral and precancerous cancer were considered potentially admissible, no restrictions were applied in relation to the year of publication and based on the language provided that an abstract in English is available. literature reviews were excluded and were used only as sources for bibliographic research.

Source of evidence screening and selection: The search for eligible articles and reports was conducted by 2 reviewers) with a 3 reviewer with the task of choosing whether to include the studies, in situations of conflict.
The 2 reviewers after having established in agreement: the eligibility criteria, the keywords and the databases to be used; they independently performed the search for articles and reports, reporting on tables the number of articles obtained for each key-word and for each database used; Studies that resulted in duplicates from different databases were deleted using the EndNote 9 software, study overlays that could not be uploaded to EndNote were manually removed by the authors after the screening phase. The 2 reviewers then proceeded to the screening and inclusion of the studies with the comparison and debate on the studies to be included.

Data management: The characteristics and type of data to be extracted from the studies was jointly decided by the 2 reviewers immediately after the study selection phase; the data concerned: the first author, the year of publication, the bibliographic reference, the type of study, the type of oral carcinoma investigated, the cell lines tested, the type of active ingredient tested, the main results and conclusions of the study. The data were extracted independently by the 2 reviewers in 2 different tables and subsequently compared and reported in a 3 table with 3 reviewers who verified the correct insertion of the data.

Language restriction: Only clinical studies in English.

Country(ies) involved: Italy.

Keywords: Oral cancer; Punica Granatum; Pomegranate; OSCC.

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