Physician Attitudes and Perceptions of Complementary and Alternative Medicine (CAM): A Multicentre Italian Study

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Purpose: Complementary and Alternative Medicine (CAM) interventions are widely used by patients with chronic disorders, including cancer, and may interact with cancer treatment. Physicians are often unaware of this, probably due to poor patient-physician communication on CAM. The purpose of this study was to evaluate physicians’ knowledge, attitudes and practice patterns regarding CAM in a survey conducted in Italy.

Methods: A questionnaire was administered to 438 physicians (11 Italian hospitals) who predominantly treat patients with chronic disease, to collect personal and professional data and information on attitudes toward CAM and its possible role in Conventional Medicine (CM).

Results: Of the 438 participants, most were specialists in oncology (18%), internal medicine (17%), surgery (15%), and radiotherapy (11%). Most worked at university (44%) or research hospitals (31%). Forty-two percent of participants believed that CAM could have an integrative role within CM. Oncologists were the physicians who were best informed on CAM (58%). Physicians working at research institutes or university hospitals had a greater knowledge of CAM.
than those employed at general hospitals ($p < 0.0001$), and those who were also involved in research activity had a greater knowledge of CAM than those who were not ($p < 0.003$). Length of work experience was significantly related to CAM knowledge. Moreover, 55% of participants suggest CAM interventions to their patients and 44% discuss CAM with them. The best-known interventions were acupuncture, Aloe vera and high-dose vitamin C.

**Conclusion:** CAM use by patients with chronic disease and/or cancer has become a topical issue for the scientific community and for physicians. Knowing the reasons that prompt these patients to use CAM and guiding them in their decisions would improve treatment and outcomes and also benefit healthcare systems. Our findings contribute to a greater understanding of CAM knowledge, attitudes, and practice among Italian physicians. Further research is needed to identify the more effective CAM treatments and to work toward an integrated healthcare model.

**Keywords:** complementary medicine, alternative medicine, physicians, cancer, treatment, Italian survey, attitudes

## INTRODUCTION

According to the U.S. National Center for Complementary and Integrative Health (NCCIH), Complementary and Alternative Medicine (CAM) therapies include a wide spectrum of practices and products, either biological (e.g., herbs or botanicals, vitamins, minerals, probiotics, homeopathic products, and Chinese herbal remedies) or non-biological (e.g., prayer, meditation, music therapy, yoga). These interventions are defined as “alternative” when they are used instead of Conventional Medicine (CM) and as “complementary” when they are used together with it (1). Their popularity has been increasing, and according to 26 studies conducted all over the world by the 1990s they were used by 7–64% of patients with chronic disorders, including cancer (2–5). In the past decade the interest in CAM has grown further, the main reasons being massive internet marketing, dissatisfaction with CM, and a desire by patients to achieve greater control over medical decisions (2).

CAM has become widespread in most industrialized countries; individuals who have used it at least once account for about 70% of the population in Canada (6), ~50% in Italy, France and Australia (7–9), 40% in the USA (3), 30% in Japan (2), and 31% in Belgium (8).

The diffusion of CAM therapies is relevant to physicians, because several biologically based approaches, such as herbs and supplements, can interfere with CM treatment efficacy, including antiblastic chemotherapy (AC) and target therapy (TT), besides heightening the risk of treatment-related toxicity and other complications. For example, St John’s wort, Asian ginseng and green tea have all been found to induce toxicity and to interact with a number of medications, including AC and TT (10–13). A study of adult cancer patients estimated that 28% were at risk of AC-herb interactions; notably, 46% of these patients were treated with curative intent (14). The interactions described between the most common AC and CAM interventions published in the English literature are reported in Table 1 (15–42). To the best of our knowledge, there are no studies in English on interactions between immunotherapy and CAM.

The wide diffusion of CAM and the attendant risk for some patients—especially those receiving active anticancer treatment (ACT)—involve that physicians should inquire about their use by patients and be familiar with the more common CAM therapies.

In a recent multicentre Italian study (7), we found that 49% of cancer patients combined CAM remedies with their ACT and that in 67% of cases the interventions were self-prescribed. Their main sources of information were the internet and the media (48%), whereas only 6% of patients received information on CAM from physicians. Critically, 85% of patients were not aware of the risk of side-effects of CAM remedies and of potential interactions with CM treatments. The latter issue raises disturbing questions and highlights the need for greater patient-physician communication on CAM. Although oncologists generally discuss treatment options with patients (choice of treatment, therapeutic targets, side-effects), they largely ignore CAM (43–45). A study conducted at the University of Texas MD Anderson Cancer Center in Houston has found limited communication and discordant views among physicians with regard to CAM therapies (46). Insufficient patient-oncologist communication on CAM has also been reported (46). Poor communication between healthcare professionals and patients has been described with regard to CAM; for instance, in a previous Italian multicentre survey, Crocetti et al. (47) highlighted a poor attitude of oncologists toward CAM. According to data published by Censis (an Italian socioeconomic research body) on fake news on medications in 2017, 28% of Italians who have a medical problem consult primarily “Dr Google,” likely due to poor or no communication with their physicians (48).

The medical education of Italian physicians is evidence-based. Most have never been taught CAM at any stage of their training, a fact that may be ascribed to lack of significant scientific evidence for its effectiveness. Indeed, the current literature on CAM and cancer is largely based on the patients’ standpoint, whereas papers
| CAM agents                                | Metabolic pathway | Interaction with cancer treatments                                                                 | Adverse events                                                                 | Reference |
|------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-----------|
| Active hexose-correlated compound        | CYP2D6 induction  | May reduce the activity of ADM, which is a substrate of this enzyme, and of Als                      | Diarrhea and itching                                                           | (15)      |
| isolated from shiitake mushrooms         |                   |                                                                                                    |                                                                                |           |
| Ananas Pineapple (bromelain)             | CYP2C9 inhibition  | Risk of overdosage in patients treated with TXL                                                    | Exacerbation of hand and foot syndrome                                          | (16)      |
| β-carotene                               |                   | Alcohol consumption has an adverse effect on β-carotene activity                                    | The hepatotoxic effects of ethanol may be potentiated by high-dose β-carotene    | (17)      |
| B-elemene (terpene from Rhizoma zedoariae and mint) |                   | Increased DDP and taxane activity                                                                  | No adverse events recorded                                                      | (18)      |
| Bitter melon (Momordica charantia)       | P-gp and CYP2C9 inhibition | Increased intracellular concentration VBL and TXL                                                | No adverse events were recorded                                                 | (19)      |
| Turmeric (Curcuma longa)                 | Weak CYP1A2, CYP2B6, CYP2C9, and CYP2D6 inhibition | Risk of overdosage in patients treated with bendaemustine and inefficacy of produgs (CTX, TAM) | Allergic dermatitis and bile duct obstruction                                   | (20)      |
| Cannabinoids                             | CYP2C9 induction  | Risk of overdosage in patients treated with produgs (CTX, TAM)                                     | Gastrointestinal complaints                                                     | (21)      |
| Di Bella multitherapy§                   | GH inhibition, enhances IGF-binding protein-1 secretion | The opioid antagonist properties of somatostatin reduce the analgesic effect of opioids in patients with advanced cancer | Gastrointestinal complaints, cholelithiasis, and hyperglycaemia                  | (22)      |
| Echinacea                                | Potent CYP3A4 inhibition | Improved pharmacokinetics of CTX, DAS, TXT, ERL, IMT, SOR (weak) VALK (high), and VP16            | Severe thrombocytopenia in a patient receiving VP16                             | (23)      |
| Essiac*                                  | CYP3A4 inhibition  | Risk of overdosage in patients treated with BTZ, DAS, TXT, ERL, IMT, SOR, VALK                      | Gastrointestinal complaints                                                     | (24)      |
| Folic acid                               | MTHFR-enhancing activity | Improved activity of antimetabolite drugs (5-Fu)                                                 | Concurrent use of folic acid may antagonize the effects of certain anticonvulsants | (25)      |
| Glucans from mushrooms*                  | EGFr and mTOR inhibition | May antagonize TAM in patients with estrogen-positive breast cancer                               | Immunosuppressive effects                                                      | (26)      |
| Green tea                                | CYP3A4 inhibition  | Similar to Essiac                                                                                    | High ALT levels                                                                | (27)      |
| Ginkgo biloba                            | CYP3A4, CYP2C19, P-gp | Similar to Essiac                                                                                    | Nervousness                                                                    | (28)      |
| Ginseng                                  | CYP3A4 inhibition  | Increased risk of IMT hepatotoxicity                                                                 | High ALT levels                                                                | (29)      |
| Glutathione                              | GSH, GSTP1        | Increased AC detoxification                                                                         | Mucosal hypersecretion                                                         | (30)      |
| Grapefruit (including juice)             | CYP3A4 inhibition  | Not recommended during ADM due to oxidations                                                        | Gastrointestinal complaints                                                     | (31)      |
| Liquorice                                 | weak CYP2B6, CYP3A4 inhibition | Similar to Essiac (weak)                                                                            | Hypertension, retinopathy and nephropathy                                      | (32)      |
| Milk thistle                             | Weak CYP2C8 and CYP2C9 inhibition | Risk of overdosage in patients taking CTX, TXL                                                      | No adverse events recorded                                                     | (33)      |
| Oleander                                 | P-gp and mTOR inhibition | May increase the blood levels of substrate drugs such as TKIs.                                       | Gastrointestinal complaints                                                     | (34)      |
| Omega 3                                  | p53               | Reduces platin activity                                                                              | Platin-drug resistance                                                         | (35)      |
| Ozone therapy                            | ND                | Not recommended during ADM due to oxidation                                                         | ND                                                                             | (36)      |
| Quercetin                                | Strong CYP3A4 and CYP2C19 inhibition | Similar to Essiac                                                                                  | High ALT levels                                                                | (37)      |
| Resveratrol                              | CYP3A4, CYP2D6, CYP2C9, inhibition | Protective effects against DDP- and ADM-induced cardiotoxicity, due to upregulation of SIRT1-mediated p53 deacetylation | No adverse events recorded                                                     | (38)      |
| Spirulina and blue-green algae           | CYP 1A2 and 2E1 inhibitions | Induces accumulation of drugs metabolized by these enzymes, including bendaemustine               | Increases the risk of their side effects                                         | (39)      |
addressing the physicians’ point of view are now beginning to be published. Since the attitudes toward CAM of Italian physicians who treat patients with chronic disorders, including cancer, have never been surveyed, we set out to investigate the personal and professional characteristics and CAM attitudes, knowledge, and use in a sample of physicians who predominantly treat this type of patients.

MATERIALS AND METHODS

Participants

A nationwide cross-sectional descriptive questionnaire survey was undertaken to collect data on CAM attitudes, knowledge and use by physicians. Letters of invitation were sent to 20 institutions, which included: research hospitals, universities and general hospitals, and 11 agreed to participate to the survey. Physicians were invited to complete the questionnaire by the researchers involved in the study (the chief of their department/the chief medical officer). The study was conducted in accordance with the 1964 Helsinki Declaration.

Participants were grouped into four specialty groups: (G1) "Oncology/Hematology/Pain management/Radiotherapy/Anaestheology" (40.4%); (G2) "Internal medicine/Geriatric medicine/Infectious diseases" (25.3%); (G3) "Surgical specialties" (15.1%); and (G4) Nuclear medicine/No specialty/Other (19.2%).

Questionnaire

A 41-item questionnaire was developed by two of the authors (M.B. and A.C.) based on literature data (47) and divided into 3 sections. The first section collected personal and professional data, including participant gender, age, education, medical specialty, years of experience, type and place of work in Italy (North, Center, South and Islands). The second section focused on CAM and asked questions on participants' knowledge of it; their view of its ability to be used with CM; whether they suggest CAM to patients or discuss it with them; whether and how it could be used in their patients, their trust in CM, and their personal use of CAM. The third section asked which CAM interventions were known to the participant, to which patients they would suggest CAM, the role they thought it could have, and which effects they have actually observed. In line with the literature (47), the commonly prescribed medical therapies such as support therapy (e.g., iron, vitamin D, calcium supplements) were not considered as CAM and are not included in the analysis.

Statistical Analysis

All questionnaires were coded and checked. Missing data and ambiguous responses were excluded from the analysis. Participant information was summarized in descriptive tables. Differences in participant characteristics and knowledge of CAM were analyzed by the chi-square test or Fisher’s exact test, as appropriate. The level of significance was set at $p < 0.05$. Analyses were performed with IBM SPSS Statistics 25.0 (49). The variables showing significant differences were entered into a logistic regression model to test the relationships between them (as independent variables) and the four specialty groups, to gain insight into participants’ attitudes to CAM. Odds ratios (ORs) and 95% confidence intervals (CI) were computed to test participants’ attitudes using G1 physicians as the reference category.

RESULTS

A total number of 438 participants responded, yielding an adjusted response rate of 82% (534 physicians were invited and 96 incomplete questionnaires were excluded). Participants were equally distributed among men and women and their median age was 53 years (range, 30–67). As regards education, 55.7% had a specialization, and only 5% had a Ph.D. degree; the most common specialty areas were G1 (40.4%), G2 (25.3%), G3 (15.1%), and G4 (19.2%); most participants (60.7%) worked in institutions in Southern Italy and were involved in research activity (54%) (Table 2).

TABLE 1 | Continued

| CAM agents | Metabolic pathway | Interaction with cancer treatments | Adverse events | Reference |
|------------|------------------|-----------------------------------|----------------|-----------|
| St. John’s worth (Hypericum) | CYP3A4 induction | Improved CTX, DAS, TXT, ERL, IMT, SOR, and VALK pharmacokinetics | Headache, dry mouth, sleepiness, gastrointestinal complaints | (40) |
| Vitamin C | ND | May reduce the effectiveness of VCR, ADM, MTX, DDP, BTZ, IMT | Kidney stones | (41) |
| Zeolite | Protein kinase B inhibition | Enhances the effect of ADM due to its antioxidant properties | Pulmonary fibrosis, leukocytosis | (42) |

AC, Antiblastic chemotherapy; ADM, Doxorubicin; ALT, Alanine aminotransferase; BTZ, Bortezomb; CTX, Cyclophosphamide; CYP, Cytochrome P450; DAS, Dasatinib; DDP, Cisplatin; ERL, Erlotinib; 5-FU, Fluorouracil; IA, Aromatase inhibitors; IMT, Imatinib; MTX, Methotrexate; NA, Not available; ND, Not documented; P-gp, P-glycoprotein; SOR, Sorafenib; TAM, Tamoxifen; TXL, Paclitaxel; TXT, Docetaxel; VALK, Vinca alkaloids; VBL, Vinblastine; VCR, Vincristine; VP16, Etoposide.

Sources: http://reference.medscape.com/drug-interactionchecker and Memorial Sloan Kettering Cancer Center: https://www.mskcc.org/cancer-care/integrative-medicine/herbs/ginseng-asianreferences-24.

*Herbal mixture patented as a cancer therapy by Rene Caisse in 1920 in Canada.
§Somatostatin, Bromocriptine, Fluvoxamine, Melatonin.
◦Gastrointestinal complaints: diarrhea, vomiting, and nausea.
Slightly more than half (50.9%) knew the meaning of the CAM acronym; most (78.6%) knew about “alternative and complementary medicine,” and most (41.8%) thought that CAM could have a role in CM (Table 3).

The statistical comparisons based on specialty group are reported in Table 4. G1 physicians were more likely to work in Northern Italy (34.5%) in a research hospital (42.4%) and were more interested in CAM than the other groups (“Do you know what CAM stands for?” yes, 57.6%; “Have you ever heard about alternative and complementary medicine?” yes, 88%; “Should patients be treated exclusively with CM?” no, 52%). The distribution of physicians involved in research activity and their interest in CAM are reported in Table 5.

CAM knowledge and communication with patients were analyzed by multivariate logistic regression (Table 6). G1 physicians were significantly associated with CAM knowledge ($p < 0.0001$) and with awareness of the difference between complementary and alternative medicine ($p = 0.01$). The lack of an association between G1 physicians and CAM suggestion and prescription to their patients explains their poor propensity for CAM interventions ($p = 0.4$ and 0.09, respectively). About half of participants stated that they do not discuss CAM with their patients.

The CAM interventions best known to our sample of physicians (Figure 1) were acupuncture (60.7%), Aloe vera
### TABLE 4: Physicians’ characteristics and their CAM knowledge according to their specialty.

| Characteristics                               | Specialty group                                                                 |
|-----------------------------------------------|--------------------------------------------------------------------------------|
|                                               | G1 Oncology, hematology, pain management, radiotherapy, anaesthesiology | G2 Internal medicine, geriatric medicine, infectious diseases | G3 Surgical specialties | G4 Nuclear medicine, no specialization, other |
|                                               | No. (%)                        | No. (%)                        | p-value 1*  | No. (%)                        | No. (%)                        | p-value 2*  | No. (%)                        | p-value 3*  |
| Gender                                        |                                 |                                 | 0.5        |                                 |                                 | 0.06        |                                 | 0.2         |
| Female                                        | 88 (49.7)                       | 59 (53.2)                       | 0.5        | 24 (36.4)                       | 49 (58.3)                       | 0.6         | 24 (36.4)                       | 49 (58.3)   |
| Male                                          | 89 (50.3)                       | 52 (46.8)                       |            | 42 (63.6)                       | 35 (41.7)                       |            | 42 (63.6)                       | 35 (41.7)   |
| Age                                           | 0.001                           |                                 | 0.6        |                                 |                                 | 0.6         |                                 | 0.6         |
| < 40 years                                    | 66 (37.3)                       | 66 (59.5)                       | 0.001      | 29 (43.9)                       | 28 (33.3)                       | 0.001       | 29 (43.9)                       | 28 (33.3)   |
| 40–65 years                                   | 107 (60.5)                      | 43 (38.7)                       |            | 35 (53)                         | 55 (65.5)                       |            | 35 (53)                         | 55 (65.5)   |
| 65 years                                      | 4 (2.3)                         | 2 (1.8)                         |            | 2 (3)                           | 1 (1.2)                         |            | 2 (3)                           | 1 (1.2)     |
| Time elapsed since specialization              | <0.0001                         |                                 | 0.1        |                                 |                                 | 0.5         |                                 | 0.5         |
| < 5 years                                     | 39 (23.2)                       | 51 (52.6)                       |            | 8 (16.7)                        | 20 (23.8)                       |            | 8 (16.7)                        | 20 (23.8)   |
| 5–10 years                                    | 36 (21.4)                       | 5 (5.2)                         |            | 6 (12.5)                        | 23 (27.4)                       |            | 6 (12.5)                        | 23 (27.4)   |
| ≥ 10 years                                    | 93 (55.4)                       | 41 (42.3)                       |            | 34 (70.8)                       | 41 (48.8)                       |            | 34 (70.8)                       | 41 (48.8)   |
| Workplace location                            | <0.0001                         |                                 | 0.8        |                                 |                                 | 0.8         |                                 | 0.8         |
| Northern Italy                                | 61 (34.5)                       | 17 (15.3)                       |            | 21 (31.8)                       | 26 (31)                         |            | 21 (31.8)                       | 26 (31)     |
| Central Italy                                 | 20 (11.3)                       | 9 (8.1)                         |            | 7 (10.6)                        | 11 (13.1)                       |            | 7 (10.6)                        | 11 (13.1)   |
| Southern Italy                                | 96 (54.2)                       | 85 (76.6)                       |            | 38 (57.8)                       | 47 (58)                         |            | 38 (57.8)                       | 47 (58)     |
| Institution                                   | <0.0001                         | <0.0001                         | 0.004      |                                 |                                 |            |                                 |            |
| Research hospital                             | 75 (42.4)                       | 8 (7.2)                         |            | 15 (22.7)                       | 36 (42.9)                       |            | 15 (22.7)                       | 36 (42.9)   |
| University                                    | 47 (26.6)                       | 72 (64.9)                       |            | 39 (59.1)                       | 36 (42.9)                       |            | 39 (59.1)                       | 36 (42.9)   |
| General hospital                              | 55 (31.1)                       | 31 (27.9)                       |            | 12 (18.2)                       | 12 (14.3)                       |            | 12 (18.2)                       | 12 (14.3)   |
| Are you involved in research activity?        | 0.001                           |                                 | 0.9        |                                 |                                 | 0.9         |                                 | 0.9         |
| Yes                                           | 106 (59.9)                      | 44 (39.6)                       |            | 40 (60.6)                       | 50 (59.5)                       |            | 40 (60.6)                       | 50 (59.5)   |
| No                                            | 71 (40.1)                       | 67 (60.4)                       |            | 26 (39.4)                       | 34 (40.5)                       |            | 26 (39.4)                       | 34 (40.5)   |
| Do you know what CAM stands for?              | 0.01                            |                                 | 0.1        |                                 |                                 | 0.3         |                                 | 0.3         |
| Yes                                           | 102 (57.6)                      | 47 (42.3)                       |            | 31 (47)                         | 43 (51.2)                       |            | 31 (47)                         | 43 (51.2)   |
| No                                            | 75 (42.4)                       | 64 (57.7)                       |            | 35 (53)                         | 41 (48.8)                       |            | 35 (53)                         | 41 (48.8)   |
| Have you ever heard about alternative and complementary medicine? | <0.0001                         | <0.0001                         | 0.03       | 0.001                           |                                 |            |                                 |            |
| Yes                                           | 154 (88)                        | 78 (70.3)                       |            | 50 (76.9)                       | 60 (71.4)                       |            | 50 (76.9)                       | 60 (71.4)   |
| No                                            | 21 (12)                         | 33 (29.7)                       |            | 15 (23.1)                       | 24 (28.6)                       |            | 15 (23.1)                       | 24 (28.6)   |
| Should patients be treated exclusively with CM? | 0.1                             |                                 | 0.06       | 0.02                            |                                 |            |                                 |            |
| Yes                                           | 58 (32.8)                       | 41 (36.9)                       |            | 32 (48.5)                       | 28 (33.3)                       |            | 32 (48.5)                       | 28 (33.3)   |
| No                                            | 92 (52)                         | 46 (41.4)                       |            | 24 (36.4)                       | 32 (38.1)                       |            | 24 (36.4)                       | 32 (38.1)   |
| I don’t know                                  | 27 (15.3)                       | 24 (21.6)                       |            | 10 (15.2)                       | 24 (28.6)                       |            | 10 (15.2)                       | 24 (28.6)   |
| Do you suggest CAM to your patients?          | 0.2                             |                                 | 0.3        | 0.6                             |                                 |            |                                 |            |
| Yes                                           | 102 (57.6)                      | 55 (49.5)                       |            | 33 (50)                         | 51 (60.7)                       |            | 33 (50)                         | 51 (60.7)   |
| No                                            | 75 (42.4)                       | 56 (50.5)                       |            | 33 (50)                         | 33 (39.3)                       |            | 33 (50)                         | 33 (39.3)   |
| Do you discuss CAM use with your patients?    | 0.2                             |                                 | 0.1        | 0.1                             |                                 |            |                                 |            |
| Yes                                           | 87 (49.2)                       | 51 (45.9)                       |            | 25 (37.9)                       | 30 (35.7)                       |            | 25 (37.9)                       | 30 (35.7)   |
| No                                            | 74 (41.8)                       | 55 (49.5)                       |            | 37 (56.1)                       | 46 (54.8)                       |            | 37 (56.1)                       | 46 (54.8)   |
| I don’t know                                  | 16 (9)                          | 5 (4.5)                         |            | 4 (6.1)                         | 8 (9.5)                         |            | 4 (6.1)                         | 8 (9.5)     |
(57.1%), and high-dose vitamin C (40.6%); the least known were Hamer’s method (12%) and *Rophalurus junceus* (poison of the blue scorpion, marketed as “Escozul”) (8.3%). We decided to exclude from this list the medical therapies that are usually prescribed as support therapy (iron, vitamin D, and calcium supplements).

The patients to whom participants would recommend CAM therapies (Figure 2) are those with cancer and chronic disease (similar percentages). A significant association was found for none of the specialty groups.

As regards the possible use of CAM (Figure 3), G1 physicians would not recommend their cancer patients to treat their disease with CAM alone (10%) but would recommend it as a support treatment (55%) during AC, whereas G4 physicians would recommend CAM as a ACT (60%). Most (33%) G2 and G3 physicians consider CAM as useless and expensive.

**DISCUSSION**

In recent years the interest in CAM has mounted considerably due to media influence and to internet marketing, besides patients’ desire to gain greater control on their treatment. The available data suggest that although 29–91% of chronic and cancer patients use CAM remedies together with their treatment, less than half of physicians, and especially of oncologists, discuss them with their patients (4, 5, 7). CAM has largely been ignored by physicians for at least 30 years and has only recently begun to attract the attention of the scientific community and of healthcare institutions.

This study surveyed the CAM knowledge, use, perception, and attitudes of Italian physicians who predominantly treat patients with chronic disease, including cancer. Although 44% of participants believe that patients should be treated exclusively with CM, most (59%) replied that they accept and prescribe CAM interventions. The patients to whom they would prescribe CAM are predominantly those with cancer (76%) or chronic disease (74%) as well as terminally ill (49%) and elderly patients (47%). Moreover, 45% (*p < 0.005*) of those surveyed believed that CAM could have a role in CM as a complementary therapy in a context of integrative medicine (IM), as also found by several studies (20, 50–55). Indeed, IM models for cancer patients are applied in hospital setting in several countries (56–59). The analysis of physicians’ characteristics highlighted that 40% of our sample are involved in treating cancer patients and work at a university (44%) or a research hospital (31%). Awareness of CAM was acknowledged by 60% of oncologists, by 42% of internal medicine specialists and 45% of “other” specialists; their different knowledge may be due to the widespread use of CAM remedies by cancer patients. This 60% of oncologists constitutes a significant improvement on the 48% described by Crocetti et al. (47) in 1996 and reflects a much greater awareness and knowledge of CAM, a greater attention to the problem and an increased use of CAM in Italy. Participant age (40–65 years) and years of practice (>10 years) were found to be significantly associated with CAM knowledge (respectively, *p < 0.001* and *p < 0.002*); a similar finding has been reported in a recent national survey of China’s oncologists (60). As expected, the physicians with a more limited knowledge of CAM were less likely to discuss it with patients, as also noted by other researchers (61). A recent Norwegian study of cancer patients who use complementary medicine suggests that poor communication experiences with physicians may result in the adoption of CAM interventions, and in some cases in postponement or reduction of the conventional cancer treatment; in contrast, positive communication experiences led to CAM use as a supplement rather than as an alternative to CM (62). Effective...
TABLE 5 | CAM knowledge in relation to participants’ involvement in research activity.

| Are you involved in research activity? | p-value |
|----------------------------------------|---------|
| Yes                                    | No      |
| 120 (50)                               | 103 (52) |

0.6

Have you ever heard about alternative and complementary medicine?

| Yes                                    | No      |
| 199 (82.9)                             | 143 (73.3) |

0.01

Are you aware of the difference between complementary and alternative medicine?

| Yes                                    | No      |
| 152 (63.6)                             | 106 (53.8) |

0.04

Do you suggest CAM to your patients?

| Yes                                    | No      |
| 143 (59.6)                             | 98 (49.5) |

0.03

Could CAM have a role in CM?

| Yes                                    | No      |
| 109 (45.4)                             | 74 (37.4) |

0.02

Do you discuss CAM use with your patients?

| Yes                                    | No      |
| 108 (45)                               | 85 (42.9) |

0.1

Specialty group

| G1: Oncology, Hematology, Pain management, Radiotherapy, Anaesthesiology | G2: Internal medicine, Geriatric medicine, Infectious diseases | G3: Surgical | G4: Nuclear medicine, No specialization, Other |
|------------------------------------------------------------------------|-------------------------------------------------------------|-------------|---------------------------------------------|
| 106 (44.2)                                                             | 71 (35.9)                                                   | 40 (16.7)   | 50 (20.8)                                   |

0.003

Bold values indicate statistically significant p-value.

TABLE 6 | Odds ratio (OR) and 95% confidence intervals (CIs) computed to assess the attitudes toward CAM of G1 physicians (specialties: Oncology, Hematology, Pain management, Radiotherapy, Anaesthesiology).

| Do you know what CAM stands for? | p-value |
|-----------------------------------|---------|
| Yes                               | 1.52 (1.02–2.25) | 0.004 |
| No                                | 1.00 (Reference category) |

Have you ever heard about alternative and complementary medicine?

| Yes | No |
|-----|----|
| 2.64 (1.54–4.52) | 1.00 |

<0.0001

Are you aware of the difference between complementary and alternative medicine?

| Yes | No |
|-----|----|
| 1.77 (1.18–2.68) | 1.00 |

0.006

Do you suggest CAM to your patients

| Yes | No |
|-----|----|
| 1.16 (0.79–1.72) | 1.00 |

0.4

Have you ever prescribed CAM to your patients?

| Yes | No |
|-----|----|
| 1.47 (0.93–2.32) | 1.00 |

0.09

<Logistic regression model adjusted for age, gender, area of origin and workplace.

Bold values indicate statistically significant p-value.

healthcare system due to shorter hospital stays and fewer drug prescriptions. In addition, various studies indicate that better educated patients with higher than average incomes are more likely to choose CAM and are frequently supported in this choice by their GPs (7, 64–66). Informing physicians about the high prevalence of CAM use and the commonly used CAM interventions has the potential to advance communication with patients. Our survey found that half of physicians discuss the role of CAM with their patients: these physicians are those who are involved in research work, have more than 10 years of specialization and belong to G1 group.

The need for improving physicians’ CAM knowledge and communication with patients has also been highlighted in recent studies by the Working Group Prevention and Integrative Oncology of the German Cancer Society (54), the German society for Palliative Medicine (67), other German institutions (68, 69) and the national survey of China’s oncologists (60). The German studies also indicate that some CAM practices (psycho-oncology, sport, micronutrient supplements) are more popular in Germany than in Italy.

Negative experiences related to physician-patient interactions and CM outcomes can encourage cancer patients to use CAM and to refuse or postpone CM (70).

In our survey, the physicians working at a university and/or a research hospital knew CAM significantly better than those who worked at a general hospital (p < 0.0001), and those who were also involved in research work knew CAM better than those who did no research (p < 0.003). Similar results are
reported in the national survey of Chinese oncologists: those working in metropolitan areas and academic hospitals have a greater knowledge of and a more favorable attitude toward CAM (60). Interestingly, in our survey 60% of the physicians involved in research would suggest CAM to patients, and 45% of them discuss it with them; surprisingly, this is also the proportion of physicians who do no research \((p < 0.1)\). Our survey demonstrated that the lack of communication about CAM between physicians and patients is not necessarily related to physicians’s knowledge of CAM. The CAM interventions best
known to participants were acupuncture (60.7%), Aloe vera (57.1%), high-dosage vitamin C (40.6%), and yoga (36.1%), whereas the least known was Escozul (8.3%). Surgeons were the physicians with the most limited CAM knowledge. All physicians stated they would prescribe CAM chiefly to patients with cancer and/or chronic disease; 33% of internal medicine physicians feel that CAM is useless and expensive, 50% of oncologists think that CAM remedies could be used as supplements, and 47% of them consider CAM useful as support in chronic treatments. Notably, most (55%) G1 physicians view CAM as a support treatment during ACT and only 10% believe that it can be used as an ACT. Interestingly, 30 and 60% of G2 and G4 physicians, respectively, believe that CAM can have a role as an ACT. Such widely different views could be related to lack of CAM training in the medical degree course. Similar to our oncologists, the national survey found that China’s oncologists accept CAM (44.9% of participants) to manage the most common symptoms related to cancer treatment such as lack of appetite, fatigue and sleep disorder (60), i.e., as support treatment. Moreover, 22% of G1 and 33% of G2 and G3 physicians consider CAM expensive and useless. To improve CAM knowledge, most U.S. medical schools (64%) are offering alternative medicine courses (69, 71). Moreover, a recent study has reported that 95% of students in an Arabic medical school were satisfied with a course on integrative and prophetic medicine (72). These data indicate an increasing need for greater insight into CAM interventions, mostly for use with CM.

In conclusion, our survey provides up to date information about physician’s knowledge of CAM and their attitudes to it. The CAM awareness of Italian physicians has considerably improved since the late 1990s, when a similar questionnaire was distributed, and their attitudes have changed accordingly. Although it is difficult to assess their CAM knowledge, attitudes and practice patterns and their true prevalence, we believe that this survey provides new and topical information. Since in Italy the question is increasingly being discussed by the medical and the lay community alike, this study provides a long overdue update on a highly topical issue.

**PERSPECTIVES**

The lack of CAM knowledge by physicians and their limited communication with patients have negative consequences on and implications for clinical management and outcomes. Notably, it has been demonstrated that the use of CAM instead of CM was associated with worse five-year survival in cancer patients (73). The use of CAM by cancer patients is therefore an outstanding issue that warrants greater attention by the scientific community and physicians. Critically, its unguided use by patients with chronic disease and/or cancer has important implications for healthcare services and care providers as well as for the patients themselves. Assessing the soundness of CAM information sources and improving communication with physicians on this topic is crucial to enhance or preserve patient health and to strengthen the therapeutic relationship and patient compliance. We believe that physicians should expand their knowledge of CAM interventions, beneficial effects and potential interactions and toxicity. Indeed, an earlier pilot study (74) has identified 47 different potential interactions among 136 herb-drug combinations whereas a more recent investigation has found that 37.2% of patients were at risk of interaction between CM and CAM interventions (75). This risk can be reduced by improving physician-patient communication, as shown by several studies (50–55, 76, 77), as well as by the
adoption of an integrative medicine model. It would be useful to run clinical trials on some interventions, like mushrooms, mistletoe, ozone, and high-dose vitamin C, for which there is some scientific evidence (78–87). It is essential to find an evidence base for CAM therapies using suitable, sensitive approaches. Discussion of CAM interventions and guidance on potential benefits and toxicities is a task that physicians should urgently undertake. Extensive research is required to assess actual CAM use and dosage in patients receiving different treatments and to work toward achieving an integrated model of healthcare provision, which should also inform EU legislation.

DATA AVAILABILITY STATEMENT
The datasets generated for this study are available on request to the corresponding author.

REFERENCES

1. Definition of Complementary and Alternative Medicine (CAM) according to the National Center for Complementary and Integrative Health. Available online at: https://nccih.nih.gov/health/integrative-health (accessed April 16, 2020).

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AUTHOR CONTRIBUTIONS

MB, RT, RD, ACr, and GF conceived the study. MB, LR, RT, PT, RD, GP, Gnu, ACr, and GF developed the study design. MB, PG, MC, ACr, and GF oversaw the study. MB, PG, MC, RD, ACu, and GF drafted the manuscript. MB, PG, and ACr analyzed the data. All authors have read and approved the final manuscript.

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13. Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, et al. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. Eur J Clin Pharmacol. (2009) 65:331–41. doi: 10.1007/s00228-008-0610-7

14. McCune JS, Hatfield AJ, Blackburn AA, Leith PO, Livingston RB, Ellis KG. Potential of chemotherapy-herb interactions in adult cancer patients. Support Care Cancer. (2004) 12:454–62. doi: 10.1007/s00520-004-0598-1

15. D’Orta A, Del Buono A, De Monaco A, Zhiqiang P, Licito A, Di Martino S. Management and treatment of sarcopenia in fifty patients receiving chemotherapy with AHCC (active hexose correlated compound). WCRJ. (2015) 5:e1089. Available online at: https://www.wcrj.net/article/1089

16. Bhui K, Tyagi S, Prakash B, Shukla Y. Pineapple bromelain induces autophagy, facilitating apoptotic response in mammary carcinoma cells. Biofactors. (2010) 36:476–82. doi: 10.1002/bif.121

17. Schuurman AG, Goldbohm RA, Brants HA, van den Brandt PA. A prospective cohort study on intake of retinol, vitamins C and E, and carotenoids and prostate cancer risk (Netherlands). Cancer Causes Control. (2002) 13:573–82. doi: 10.1023/A:1016332208339

18. Li QQ, Wang G, Zhang M, Cuff CE, Huang L, Reed E. Jeta-Elemene, a novel plant-derived antineoplastic agent, increases cisplatin chemosensitivity in lung tumor cells by triggering apoptosis. Oncol Rep. (2009) 22:161–70. doi: 10.3892/or_00000420

19. Pitchakarn P, Ohnumpa S, Pritha K, Pompimun W, Ambudkar SV, Limtrakul P. Kuguacian J isolated from Moromadica charantia leaves inhibits P-glycoprotein (ABCBl)-mediated multidrug resistance. J Nutr Biochem. (2012) 23:76–8. doi: 10.1016/j.jnutbio.2010.11.005

20. Sannmukhani J, Satovia V, Trivedi J, Patel T, Tiwari D, Panchal B, et al. Efficacy and safety of curcumin in major depressive disorder: a randomized controlled trial. Phytother Res. (2014) 28:579–85. doi: 10.1002/ptr.5025

21. Scott KA, Dalgleish AG, Liu WM. Anticancer effects of phyto cannabinoids used with chemotherapy in leukaemia cells can be improved by altering the sequence of their administration. Int J Oncol. (2017) 51:369–77. doi: 10.3892/ijo.2017.4022

22. Todisco M, Casaccia P, Rossi N. Cyclophosphamide plus somatostatin, bromocriptine, retinoids, melatonin and ACTH in the treatment of low-grade non-Hodgkin’s lymphomas at advanced stage: results of a phase II trial. Cancer Biother Radiopharm. (2001) 16:171–7. doi: 10.1089/108497801300189263

23. Litasos G, Eleftheriotis I, Todorova R, Moulakakis A. Severe thrombotic thrombocytopenic purpura (TTP) induced or exacerbated by the immunostimulatory herb Echinacea. Am J Hematol. (2006) 81:224. doi: 10.1002/ajh.20531

24. Eberding A, Madera C, Xie S, Wood CA, Brown PN, Guns ES. Evaluation of the antiproliferative effects of Essiac on in vitro and in vivo models

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