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Sertraline repositioning: an overview of its potential use as a chemotherapeutic agent after four decades of tumor reversal studies

João Luiz Baú-Carneiro [a], Isabela Akemi Guirao Sumida [a], Malu Gallon [a], Tânia Zaleski [b,c,d], Marianna Boia-Ferreira [e], Francelise Bridi Cavassin [b,*]

[a] Medical School Undergraduate Program, Faculdades Pequeno Príncipe (FPP), Curitiba, Brazil
[b] Faculty of Medical Sciences, Faculdades Pequeno Príncipe (FPP), Curitiba, Brazil
[c] Faculty of Biological Sciences, Universidade Estadual do Paraná (UNESPAR), Paranaguá, Brazil
[d] Post Graduate Program of National Network's in Education, Universidade Federal do Paraná (UFPR), Curitiba, Brazil
[e] Postdoctoral Program of Cellular and Molecular Biology, Universidade Federal do Paraná (UFPR), Curitiba, Brazil

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ABSTRACT

Sertraline hydrochloride is a first-line antidepressant with potential antineoplastic properties because of its structural similarity with other drugs capable to inhibit the translation-controlled tumor protein (TCTP), a biomolecule involved in cell proliferation. Recent studies suggest it could be repositioned for cancer treatment. In this review, we systematically map the findings that repurpose sertraline as an antitumoral agent, including the mechanisms of action that support this hypotesis. From experimental *in vivo* and *in vitro* tumor models of thirteen different types of neoplasms, three mechanisms of action are proposed: apoptosis, autophagy, and drug synergism. The antidepressant is able to inhibit TCTP, modulate chemotherapeutical resistance and exhibit proper cytotoxicity, resulting in reduced cell counting (*in vitro*) and shrunken tumor masses (*in vivo*). A mathematical equation determined possible doses to be used in human beings, supporting that sertraline could be explored in clinical trials as a TCTP-inhibitor.

Introduction

About nine million people die from cancer each year, being considered the second leading cause of death in the world [1]. In this context, non-cancer drugs are thoroughly reviewed for possible effects on cell proliferation, aiming to reposition them for therapeutic use in clinical practice [2,3]. A group that has been recurrently the target of studies with encouraging results are the psychotropic drugs [4–7]. Among them, the selective serotonin reuptake inhibitor (SSRIs) sertraline stands out [8,9].

Sertraline hydrochloride was approved in 1991 for the treatment of various psychiatric disorders [10], nowadays it is considered first-line for managing depression in America [11]. Afterwards, it was in 1993 that Adam Telerman and Robert Amson set the starting point for discovering the anti-tumor properties of this antidepressant [12]. Structurally, its molecule was found to be similar to other drugs capable to inhibit Translationally Controlled Tumor Protein (TCTP), a biological compound present in eukaryotic stem cells in varying amounts [13]. A great number of biological activities are credit to TCTP, including anti-apoptotic action and involvement in cell stress pathways [14]. Furthermore, years after its discovery, Telerman et al. [12] identified this protein as an important protagonist in the tumor reversal process.

Because of the importance of this protein in maintaining cell death and survival pathways in addition to evidence linking it to cancer pathophysiology [15–18], it was proposed that reducing TCTP levels could be a promising target in cancer therapy [19]. Because of it ability of secreting histamine, antihistamines and other structuraly simmilar molecules such as antipsychotics and antidepressants were used in an attempt to inhibit TCTP. Of the drugs tested, sertraline obtained the best results, increasing the number of reversible clones in tumor lines by 30%, a result attributed to the down-regulation of TCTP [19]. In addition, experimental studies support that the antidepressant is effective in neoplasms therapeutics as it has specific antitumor characteristics [8, 20, 21] whereas case reports suggested that the use of sertraline could improve the clinical status of patients and even induce tumor remission [9,22].

Therefore, with evidence that sertraline can play an important role as a chemotherapeutic agent, the present study aimed to provide a short

* Corresponding author at: Faculty of Medical Sciences, Faculdades Pequeno Príncipe (FPP), 333, Iguaçu Avenue, Curitiba, Paraná, Brazil.
E-mail address: francelise.cavassin@professor.fpp.edu.br (F. Bridi Cavassin).

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overview of the four decades of tumor reversal studies, including the discovery of TCTP, and to map and synthesize the mechanisms of anti-tumor action attributed to sertraline, a known TCTP-inhibitor, which are essential to support future drug repositioning trials.

TCTP: a viable target for cancer treatment

TCTP is a protein which gene (tpt1) is composed of approximately 4000 nucleotides [23] and is present in eukaryotic stem cells [13]. It's structure was first described by Susan MacDonald in 1995, being called the histamine-releasing factor (HRF), because of its ability to release histamine [24]. Subsequently, other biological activities were identified: maintenance of homeostasis and cell survival (anti-apoptotic action and involvement in cell stress pathways), cell cycle and development (action on microtubules and embryonic development), regulation of cell growth, protein synthesis and degradation, as well as extracellular actions as a signaling molecule in immunological reactions [14]. Few years later, Telerman et al. [12] identified TCTP and SIAH-1 as important protagonists in the tumor reversal process - characterized by the ability of some neoplastic cells to revert their malignant phenotype to one closer to normal. The tumor reversion triggered by such molecules can be summed upby three distinct mechanisms: (1) inhibition of tpt1/TCTP expression, (2) activation of the SIAH-1 pathway and (3) inhibition of messenger RNA synthesis in genes that decode ribosomal proteins [25].

TCTP is linked to apoptosis thought the following mechanisms: (1) cooperation with other proteins, (2) prevention of apoptosis and (3) p53 antagonism [14] First, the cooperation occurs due to the interaction of TCTP with proteins of the Bcl-2 family (such as Bcl-xl), inhibiting the apoptosis of cells [26–30]. The prevention of apoptosis occurs by binding a specific TCTP site to a receptor on the mitochondrial surface, which competes with another pro-apoptotic protein, called Bax. Thus, TCTP antagonizes Bax and prevents activation of apoptosis [31]. In addition, TCTP can also activate Apaf-1, a protease of the apoptotic pathway that exhibits a site for protein binding, which would lead to inhibition of caspase-9 release, normally triggered by the stimulus of Apaf-1 [32].

TCTP is also related to p53 through a reciprocal antagonism [13]. TCTP reduces intracellular levels of p53 by modulating the activity of NUMB and MDM2, leading to proteasomal degradation of p53. Several forms of its regulation can occur as transcriptional repression, activation of protein kinase K (PKR) by the structure of TCTP RNA, followed by inhibition of TCTP synthesis, transcriptional activation of TSAP6 by p53, which leads to extracellular secretion of TCTP [13,18]. (See Fig. 1).

Sertraline as a promising TCTP-inhibitor

Because of the importance of TCTP for the maintenance of the path of cell death and survival and the evidences that links this protein to the pathophysiology of cancer [15–18], it was proposed that reducing its levels could be a promising target in cancer therapy [19]. Antihistamines and structurally similar molecules, such as antipsychotics and antidepressants were used to verify whether inhibition of TCTP expression would induce changes in the malignant phenotypes of different strains (colorectal, pulmonary and melanoma). Of the drugs tested, sertraline was the one that obtained the best results, therefore, it became one of the most studied drugs in tumor reversal models [19].

A specific lock-and-key interaction between sertraline and tpt1/TCTP was described by Amson et al. [18], in which the antidepressant would directly bind to tpt1/TCTP, avoiding its interaction with MDM2. Thus, promoting the interaction of TCTP autoubiquitination with MDM2 and p53, leading to MDM2 autoubiquitination and restoring p53 levels. Consequently, the reinstitution of p53 levels prevents its degradation [13,33–35].

Most of these findings were obtained during experimental studies, which sought to determine the antitumoral mechanisms and outcomes of administrating the antidepressant in tumor models. Fig. 2 and Table 1

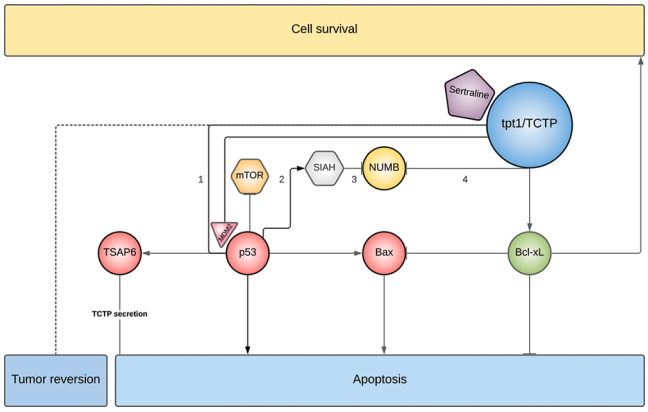

Fig. 1. Sertraline-TCTP binding results in apoptosis and tumor reversal.
Caption: Antitumoral mechanism of action of sertraline by preventing the degradation of p53 by TCTP and suppression of TCTP leading to tumor reversion. Sertraline binds directly to tpt1/TCTP, avoiding its interaction with MDM2 and, thus, promoting the interaction of TCTP autoubiquitination with MDM2 and p53, leading to MDM2 autoubiquitination and thus, restoring p53 levels. Consequently, restoring p53 levels prevents its degradation. TCTP enhances cell survival though cooperation with Bcl-xl (a protein from the Bcl-2 family) and competition against Bax (pro-apoptotic protein which synthesis is coordinated by p53, the same way as TSAP6). Other regulatory pathways are represented: (1) transcriptional repression of TCTP by p53; (2) transcriptional activation of Siah1b by P53; (3) degradation of NUMB by the Siah1b-E3; and (4) modulation of NUMB though TCTP. Bcl-2, B-cell lymphoma 2; TCTP, translationally controlled tumor protein.
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summarizes available studies, including research countries, types of neoplasm tested, settings and methods. Thirteen different types of neoplasms were assessed, on *in vitro, in vivo,* or observational studies. Breast cancer was the most investigated, representing 46.15% [13,21, 35–38], whilst experimental studies with *in vitro* or *in vivo* approaches prevailed. Only one case report and one cohort study are published [22, 39].

Sertraline antitumor action mechanisms

Three proposed mechanisms are raised: apoptosis, autophagy, and drug synergism. Fig. 3 summarizes the mapping of these mechanisms from the studies, including the types of neoplasms and outcomes presented by them.

Apoptosis

By definition, it is the process of controlled cell death that physiologically regulates cell populations through intracellular activation of enzymes that degrade their own DNA [40]. Two pathways are described: intrinsic - which involves the B-cell lymphoma 2 (Bcl-2) family and the initiating caspases 2, 8, 9 and 10 [41,42]; and extrinsic - death initiated by receptor followed by the activation of the initiating caspases and finally the executors (3, 6 and 7) [43–45]. Different mechanisms and findings were related to it, including the inhibition of TCTP [13,19, 33–35,46], interactions on the mTOR/Akt pathway [20,21,47,48], increased caspase-3 levels [26,33,46,49,50], increase on caspase-7 levels [50], ionic changes related to Ca2+ [33,51], increased expression of tumor protein P53 (p53)[33, 52], inhibition of breast tumor initiating cells (BTIC)[36, 37] and decreased expression of Bcl-2 [26].

Autophagy

Autophagy is considered a survival mechanism in times of nutrient deprivation when the cell undergoes continence stress, survives by cannibalizing itself and recycling the digested content through lysosomal enzymes [53]. The administration of sertraline was reported to

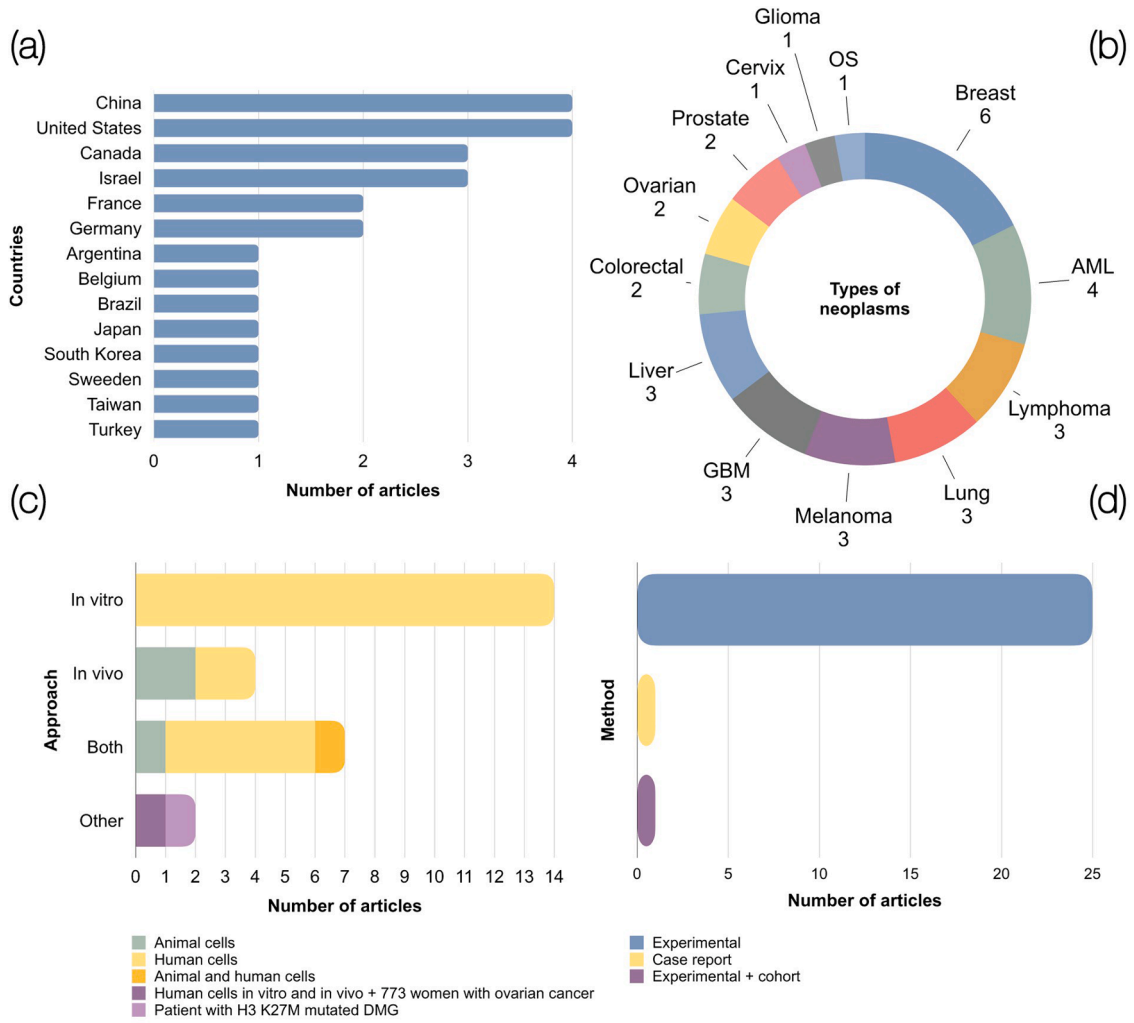

Fig. 2. Overview of included studies.
Caption: (a) Study setting; (b) Neoplasm submitted to intervention with sertraline; (c) Population according to the approach; (d) Method. AML, acute myeloid leukemia; E, experimental; DMG, diffuse midline glioma; GBM, glioblastoma multiforme; OS, osteosarcoma.
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induce autophagy in AML, lung, and prostate cancer [46,47,49]

Drug synergism

It is a drug interaction that increases the individual effect of a medication when taken together with another one. Regarding sertraline, 15 different medications are cited as synergistic: doxorubicin [21,26, 54], docetaxel [36,37], pterostilbene [55,56], the Coordinated Survival Paths Protocol (CUSP9) which involves nine medications (aprepitant, artesunate, auranofin, captopril, celecoxib, disulfiram, itraconazole, ritonavir, sertraline) [22,34], thimerosal [38], dacarbazine [33], erlotinib [47], etoposid [21], olaparib [21], sorafenib [57], vilazodone [37], vincristine [26], TNF-related apoptosis-inducing ligand (TRAIL) [58] and XL413 [48].

As for the type of synergism mechanism, summation (additive) and potentiation are reported. Concerning summation mechanisms cytotoxicity [26,46, 56] mTOR action [21] and the inhibition of BTIC's [36] are highlighted. These, taken together with chemotherapeutic drugs, would act in an additive manner aiming to destroy tumor cells. For potentiation, Drinberg et al. [54] suggested that sertraline inhibits ATP-binding cassette transporters (ABC), a family of proteins which are supposed to decrease intracellular concentrations of chemotherapies. Further interactions are still to be detailed.

Outcomes of sertraline administration in tumor settings

The most remarkable outcome of the administration of sertraline in tumor models is the reduction in tumor cell counts after sertraline intervention (Fig. 3). Other results are decreased sphere forming assay (SFA)[33, 35–37, 46, 50, 52, 55], shrunk of tumor masses [8,19,20,22, 33,36,37], decreased relapse [21,36,54], decreased Marker of Proliferation Ki67 (MKi67) levels [33,37] and near complete remission of tumor [22].

At the present, only one study associated the administration of the SSRI with a decrease in time to relapse and an increase in MKi67 levels in ovarian cancer [39]. However, the population at this observational stage was composed mostly of patients with high-grade carcinoma with serous histology (76%), characteristics linked to the worst prognosis of the disease, whereas information on the period of administration or dosage of the drug were not provided.

Discussion

Drug repositioning offers the opportunity to identify new uses for substances already well established in clinical practice. Based on new tests and experimental research, they can reveal new targets and pathways to be explored further in clinical trials. When successful, this

Table 1
Characteristics of included studies.

N	Citation	Study aims	Cell type	Intervention	Outcomes
1	Amit et al. (2009) [23]	Evaluate the effects of SSRIs compared to chemotherapy on human cells of lymphoma and AML	Human cells of lymphoma and AML	Cells were exposed to sertraline, doxorubicin vincristine and cyclophosphamide	Synergism with doxorubicin and vincristine and apoptosis
2	Amson et al. (2011) [13]	Compare the effects of antihistamines drugs and SSRIs on human tumor cells	Human cells of breast cancer	Cells were exposed to antihistamines and SSRIs and had their growth rates and TCTP levels rated	Apoptosis by TCTC inhibition
3	Boia-Ferreira et al. (2017) [41]	Evaluate the effects of sertraline on TCTP levels of melanomas	Human cells of melanoma; rats	Exposition of cells to sertraline, followed by *in vivo* evaluation	Lower tumoral growth though apoptosis by TCTC inhibition
4	Chinnapaka et al. (2020) [51]	Evaluate the anti-prostate cancer steam cells (PCSC) targeting effects of sertraline on PCSC	Human cells of PCSC	Cells were cultured with sertraline at various doses. Then, cell studies were performed	Apoptosis and autophagy by free radicals of H_2O_2, decreased TCTP and increased caspase 3
5	Christensen et al. (2016) [49]	Evaluate the effects of SSRIs on ovarian cancer cells and on overall survival of patients diagnosed with ovarian cancer	Human cells of ovarian carcinoma mice; 733 patients diagnosed with ovarian cancer	Cells were subjected to a sertraline therapy, followed by *in vivo* evaluation. A retrospective analysis based on medical records checked the use of SSRIs and evaluated the progression of ovarian cancer on patients	Cell proliferation of ovarian tumor cells and MKi67 levels. SSRIs users had a shortened time until relapse
6	Di Rosso et al. (2018) [38]	Evaluate the effects of sertraline and fluoxetine on lymphomas growth *in vivo*	Animal cells of lymphomas; mice	Cells were injected subcutaneously on mice and drugs were administered	Shrink palpable tumor masses through apoptosis
7	Drinberg et al. (2014) [48]	Evaluate the effects of sertraline on ovarian cancer	Human cells of ovarian adenocarcinoma; mice	Cells were injected subcutaneously on mice and drugs were administered	Synergism with doxorubicin; tumor regression and increased survival
8	Geeraerts et al. (2021) [36]	Repurpose sertraline and thimerosal as inhibitors of tumoral growth	Human cells of breast cancer and animal cells of AML; mice	Exposition of cells to sertraline and thimerosal, followed by *in vivo* evaluation	Synergism with thimerosal; inhibited tumor growth
9	Gil-Ad et al. (2008) [8]	Evaluate the effects of sertraline and paroxetine on colorectal cancer growth *in vivo*	Human cells of colorectal cancer; mice	Cells were inoculated on mice and drugs were administered	Apoptosis by caspase-3 pathway; shrink palpable tumor masses
10	Gwynne et al. (2017) [34]	Evaluate the effects of SSRIs on human cells of breast cancer	Human cells of breast cancer; mice	Exposition of cells to sertraline, followed by *in vivo* evaluation	Synergism with docetaxel and vilazodone increasing apoptosis; inhibited tumor growth
11	Hallett et al. (2016) [33]	Evaluate the effects of SSRIs on animal cells of breast cancer	Animal cells of breast cancer; rodents	Cells were inoculated on rodents and SSRIs were administered	Apoptosis through BTIC's, leading to inhibited cell proliferation
12	Huang et al. (2011) [50]	Evaluate the effects of sertraline on human cells of prostate cancer	Human cells of prostate cancer	Cells were treated with sertraline and cell studies were performed	Increased calcium influx, leading to apoptosis
13	Jiang et al. (2018) [39]	Evaluate the effects of sertraline on animal cells of lung cancer	Animal cells of lung cancer; mice	Cells were inoculated on mice and drugs were administered	Increased tumor cells apoptosis though mTOR pathway and autophagy
14	Kast et al. (2014) [42]	Check new approaches to GBM, according to CUSP9 protocol	Human cells of GBM	Exposition of cells to drugs, followed by *in vitro* evaluation	Increased life expectancy in GBM patients
15	Kuwahara et al. (2015) [45]	Compare the antitumor effects of SSRIs to SNRIs	Human cells of liver cancer	Cells were treated with SSRIs and SNRIs	Apoptosis; reduced cell proliferation
16	Li et al. (2017) [35]	Identify the role of TCTP on tumor cells and mechanisms of inhibition	Human cells of cervix cancer and breast cancer	Cells were submitted to drugs and/or radiotherapy	Apoptosis and decreased cell survival rate on cells treated with etoposide and sertraline
17	Lin et al. (2010) [24]	Verify if sertraline has antitumoral action	Human cells of breast cancer and lymphoma; mice	Exposition of cells to sertraline, followed by *in vivo* evaluation	Synergism with doxorubicin; increased apoptosis through mTOR pathway
18	Lin et al. (2013) [52]	Evaluate the effects of sertraline on human OS cells	Human cells of osteosarcoma	Exposition of cells to sertraline	Apoptosis through cytotoxicity
19	Reddy et al. (2008) [22]	Evaluate the effects of sertraline on human melanoma cells	Human cells of melanoma; rats	Exposition of cells to sertraline, followed by *in vivo* evaluation	Apoptosis; shrinking of tumoral masses
20	Salacz et al. (2017) [25]	Report a novel anti-cancer treatment utilizing repurposed drugs (modified CUSP/MTZ) in a patient with H3 K27M mutated diffuse midline glioma (DMG)	Patient with H3 K27M mutated DMG	First, laser thermotherapy was performed, followed by standard concurrent radiotherapy and temozolomide, followed by a modified CUSP including sertraline	Near complete remission of enhancing tumor and steady clinical improvement
21	Schmidt et al. (2013) [44]	Investigate protocols that could benefit the treatment of GBM	Human GBM cells	Cell lines were tested with 465 pairs of drugs	Synergism with pterostilbene

process can benefit the therapeutic field by saving time and resources, as well as providing a new therapeutic option for a particular disease. Our proposal was to map evidence that sertraline has the potential to be repositioned as a chemotherapeutic agent as for the probable antitumor action proposed by several studies.

From the available literature, 13 different neoplasms exposed to sertraline on experimental or observational studies presented three main mechanisms of action: apoptosis, autophagy, and drug synergism. The antidepressant played an important role in shrinking tumor masses and reducing tumor cell counting. In this context, decades of tumor reversal studies stress that these findings are reliable, as the antidepressant has shown ability to inhibit TCTP (leading to increased p53 levels and tumor reversal) [12,19,25,33], modulate chemotherapeutical resistance [54] and exhibit proper cytotoxicity [59]. A timeline was drawn to illustrate the evolution of these decades of studies aiming to repurpose the antidepressant (Supplementary Material 1).

As for the published studies, these generally involved some *in vitro* experimental stage, whereas the most reported outcome of that point

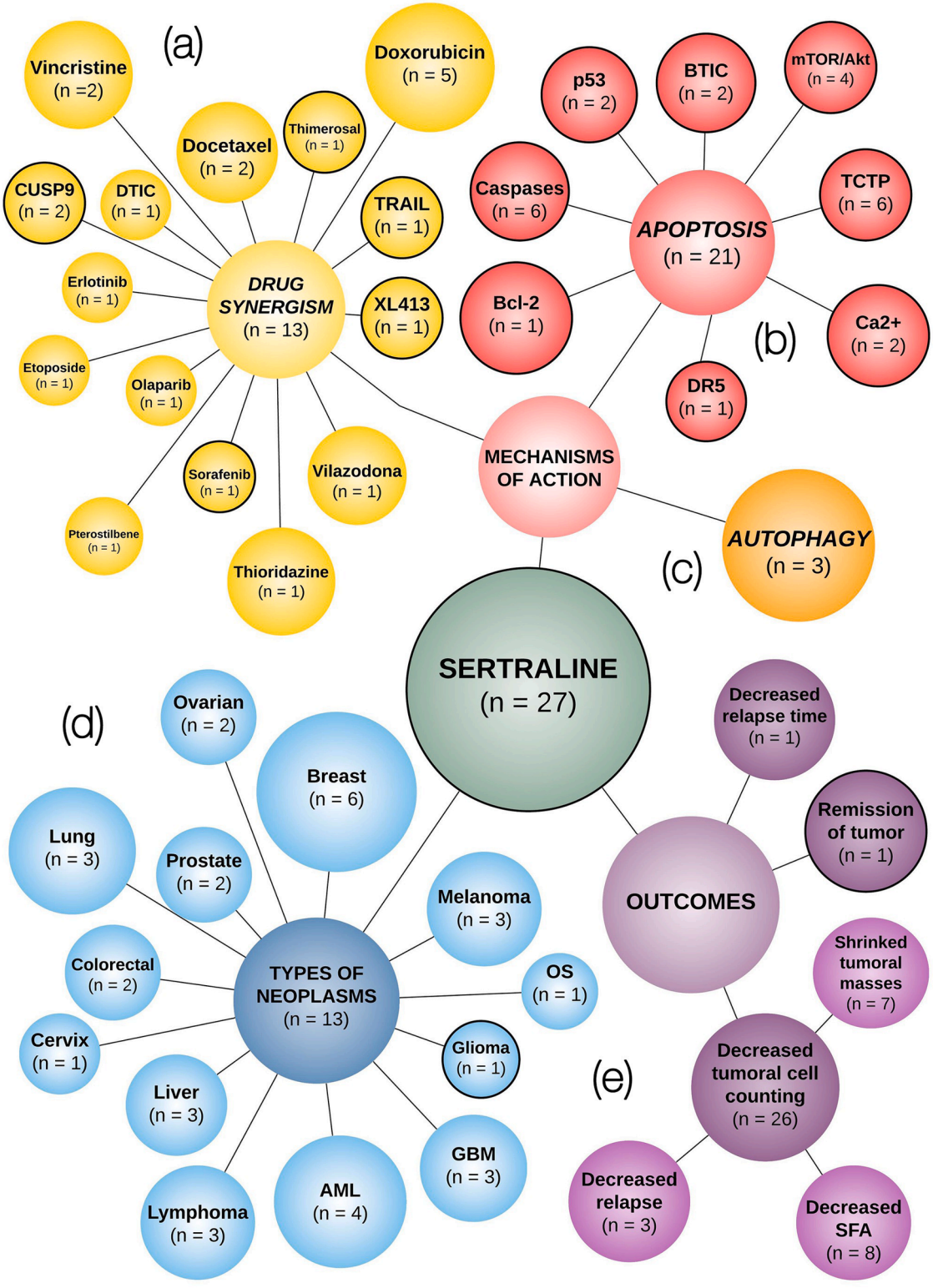

Fig. 3. Mapping of mechanisms of action, types of neoplasms and outcomes.
Caption: Mapping of mechanisms of action including (a) drug synergism, (b) apoptosis, (c) autophagy; (d) Types of neoplasms submitted to intervention with sertraline; (e) Outcomes of the intervention. AML, acute myeloid leukemia; BTIC, breast tumor initiating cell; Bcl-2, B-cell lymphoma 2; CUSP9, Coordinated Survival Paths Protocol; DTIC, dacarbazine; GBM, glioblastoma multiforme; mTOR/Akt, mammalian target rapamycin/ protein kinase B; OS osteosarcoma; SFA, sphere forming assay; TCTP, translationally controlled tumor protein.
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was a diminished cell counting in comparison to the control group after sertraline intervention, as indicated by the reduction in SFA. This result was primarily related to apoptosis and has been directly attributed to TCTP antagonism in breast [35, 52], cervical cancer [35], colorectal cancer [19], GBM [34] leukemia [19], lung [19], melanoma [19,33] and prostate [46]. Another mechanism of action that supports this outcome was autophagy, reported in AML [49], on lung [47] and prostate [46]. Furthermore, several studies reported synergism between sertraline and other drugs in *in vitro* experiments in AML [26], breast cancer [21, 35–38], cervix cancer [35], GBM [55,56], glioma [22], liver cancer [22, 48], lung cancer [50,58], lymphoma [26], and melanoma [33]. Curiously, Amit et al. [26] reported that sertraline revealed a superior antitumor effect in comparison to doxorubicin, vincristine, and cyclophosphamide ($p<0.015$). However, the best outcomes were registered with the combination of the antidepressant with doxorubicin [26].

On the other hand, of eleven *in vivo* experimental models eight reported that sertraline-treated animals had smaller tumor masses when compared to the control group [8,19–21,33,36,38,60]. In addition, three studies agreed with minimization of relapse in breast cancer [36], lymphoma [21], ovarian cancer [54], while two show a decrease in cell count when compared to the control group in lung cancer [47] and lymphoma [60]. The mechanisms of these results have been attributed to apoptosis through TCTP inhibition [19,33,46], regulation of TCTP levels through PI3-quinase/Akt/mTORC1 pathway [20,21,47,48], activation of apoptotic pathways [8], BTIC's inactivation [36,37], autophagy [47] and drug synergism [8,19–22,33,36–38,47,48,50,54, 57,58].

Regarding drug synergism, there are many reports that highlight superior outcomes of tumor cell counting reduction and tumor mass shrinkage in mixed schemes. Unfortunately, most of them do not describe the exact mechanism by which the synergism followed [21,26, 35,47,56]. All in all, Kast et al. [34] and Salacz et al.[22] reported that repositioning the empirical use of sertraline in therapeutic regimens for GBM (such as CUSP9) was beneficial, attributing the increase in patient's survival rates to these synergistic mechanisms.

Apart from its mechanism of action, the repositioning of sertraline as a therapeutic assistant in the treatment of neoplasms depends on its precise concentration in humans and on a safe toxicological profile. The concentrations administered on *in vivo* experimental studies ranged from 1 mg/kg/day [20] to 60 mg/kg/day [36], with an average of 22.14 mg/kg/day, mostly based on the IC50 of sertraline obtained in preliminary tests. When extrapolating the doses used by the authors on *in vivo* models, we obtain a variation of doses to be administered per day in humans between 9.13 mg/day to 913.2 mg/day [61], with average of 233.9 mg/day, being within the therapeutic range, which varies from 50 to 400 mg/day [62]. Only two concentrations were above 400mg: 547.9 mg/day [36] and 913.2 mg/day [47] as presented in Table 2. Therefore, we believe that the effective therapeutic regimens in reducing tumor cell

Table 2
Equivalence between doses performed *in vivo* and their substantial extrapolation on human beings [32].

N	Author	*In vivo* neoplasms	Cell Line	Animal	Therapeutics	Dose performed *In vivo*	Outcome	Extrapolation
1	*Tuynder* et al. *(2004)* [1]	Breast	MDA-MB231	*Scid/Scid* Mice	Injection once a day for 60 days	Sertraline (18 mg/kg), Promethazine (22.5 mg/kg) and Thioridazine (6.75 mg/kg)	Shrinking of tumor palpable masses	164,4 mg/day
		AML	U937		Injection once a day for 28 days			
2	*Reddy* et al. *(2008)* [2]	Melanoma	A375	Mice	Single injection	Sertraline (1 mg/day)	Shrinking of tumor palpable masses	9,13 mg/day
3	*Gil-Ad* et al. *(2008)* [3]	Colorectal	HT-29	Mice CD1	Injection twice a week for the first 3 weeks followed by 3 times a week from the third week ahead	Sertraline (15 mg/kg)	Shrinking of tumor palpable masses	137,8 mg/day
4	*Lin* et al. *(2010)* [4]	Lymphoma	Pten$^{+/-}$Eμ-Myc, Eμ-Myc/Bcl-2, and Eμ-Myc/eIF4E	Mice C57BL	Injection of doxorubicin (single dose), rapamycin (daily for 5 days) and sertraline (daily for 5 days)	Sertraline (20 mg/kg), Doxorubicin (10 mg/kg) and Rapamycin (4 mg/kg)	Reduced relapse; increased survival rate; inhibited tumoral growth	182,6 mg/day
5	*Drienberg* et al. *(2014)* [5]	Ovarian	OVCAR-8	Athymic Nude Mice	Intravenous for 3 days, 4 times a day Gavage for 3 days	Saline and Doxorubicin (2 mg/kg) Sertraline (2 mg/kg)	Reduced relapse; increased survival rate	18,2 mg/day
6	*Christensen* et al. *(2016)* [6]	Ovarian	SK-OV-3	Athymic Nude Mice	Single injection	Sertraline (10 mg/kg)	Increased cell proliferation and increased Ki67 levels	91,3 mg/day
7	*Hallet* et al. *(2016)* [7]	Breast	MMTV-Neu	Mice FVB/N	Intravenous for 7 days, once a day	Sertraline (60 mg/kg)	Shrinking of tumor palpable masses; decreased Ki67 levels; reduced relapse	547,9 mg/day
					Intravenous sertraline for 7 days (single daily dose) and single docetaxel dose on the first day	Sertraline (60 mg/kg) and Docetaxel (10 mg/kg)		
8	*Boia-Ferreira* et al. *(2017)* [8]	Melanoma	B16-F10	Mice C57BL/6	Intraperitoneal daily for 12 days	Sertraline (10 mg/kg)	Shrinking of tumor palpable masses; decreased Ki67 levels	91,3 mg/day
9	*Rosso* et al. *(2018)* [9]	Lymphoma	EL4	Mice C57BL/6 J	Gavage for 5 weeks	Sertraline (20 mg/kg/day)	Reduced tumor cells counting, reduced risk of developing a tumor	182,6 mg/day
10	*Jiang* et al. *(2018)* [10]	Lung	A549-luc	Mice NSCLC	Per oral for 6 months Per oral for 6 months	Sertraline (50 mg/kg) Sertraline (50 mg/kg) and Erlotinib (50 mg/kg/day)	Reduced tumor cells counting	913,2 mg/day
11	*Geeraerts* et al. *(2021)* [11]	Breast	MDA-MB-231, MDA-MB-468, MCF7 and HCC70	Mice NOD-SCID/IL2γ-/-	Intraperitoneal injections on days 7, 9, 11, 13, 15, 20 and 24	Sertraline (2.5 mg/kg), Artemether (40 mg/kg) or both	Inhibition of tumor growth	22,7 mg/day

Caption: Eight articles 1,2,3,4,5,6,8,9 performed doses that are equivalent to the standard approach on psychiatric disorders, whereas two articles 7,10 performed doses that exceed that therapeutic index; AML, Acute Myeloid Leukemia.
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count, reducing palpable tumor masses, and decreasing recurrences are practicable in humans.

Apart from the expected side effects of SSRI [63] and "serotonin toxicity" (provoked by up to 30 times the common daily dose) [64,65] data can be variable regarding severe symptoms, with reports of decreased level of consciousness, electrocardiographic changes, and seizures with overdoses greater than 75 times the recommended daily dose [65]. Specifically with sertraline, studies state that overdosing was not related to greater complications or morbidity, with side effects being the same as those reported with usual doses [66]. Recent reports indicate that severe cases of overdose with SSRI are increasing, but frequently happen during multiple drug abuse, especially mixed to alcohol [65,67]. Other side effects such as inhibition of platelet secretion, aggregation, and blood plug formation are under investigation, nevertheless, it is presumed, that patients with thrombocytopenia or platelet disorder could benefit from higher doses. [68]

To overcome this impasse, Lei et al. [69] synthesized a nanoliposome containing sertraline and indocyanine green (ICG), called Ser / ICG @ Lip, with the aim of increasing the concentrations administered and avoiding undesirable side effects. This technology offers a new drug delivery pathway in reason of it's targeted-specific pharmacodynamics and simplified pharmacokinetics that may improve the therapeutic effect towards tumor therapy [70,71] In addition, here we have identified more than thirteen instances of synergism with other drugs that could improve therapeutic regimens, reducing toxicity and side effects.

Conclusions

We conclude by suggesting that the direct action of sertraline on components linked to cellular dynamics can signal an active interference of this drug in tumor biogenesis. Evidence confirms that its repositioning could be explored, with probable safety and synergistic potential with other chemotherapeutic drugs currently available. We have also identified a Phase I clinical study (NCT02891278) which proposes the determination of the feasibility, safety, and toxicity of administering sertraline in combination with timed-sequential cytosine arabinoside (ara-C) in adults with relapsed and refractory acute myeloid leukemia (AML). The results will be decisive for the usefulness of repositioning sertraline in chemotherapy regimens in humans.

Credit author statement

João Luiz Baú-Carneiro and Francelise Bridi Cavassin elaborated the content and figures, structured, and wrote the manuscript up to the last version, reviewing it as to its important intellectual content. João Luiz Baú-Carneiro is himself the creator of all the figures. Isabella Akemi Guirao Sumida and Malu Gallon searched the databases for articles and wrote the first draft of the manuscript. Tânia Zaleski reviewed the article for important intellectual content and Marianna Boia-Ferreira was the specialist researcher to verify the quality of the selected studies as well as a key element in conducting the discussion.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

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Supplementary materials

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-João Luiz Baú-Carneiro is a medical student from the 12th period (6th year of medical school) and a volunteer in academic internship at a public-private oncological hospital in Curitiba-PR, Brazil.

-Isabela Akemi Guirao Sumida is a medical student from the 12th period (6th year of medical school) in Curitiba-PR, Brazil.

- Mala Gallon is a medical student from the 12th period (6th year of medical school) in Curitiba-PR, Brazil.

-Tânia Zaleski is a biologist with PhD in Zoology. Practice area in biostatistics. Post-graduate professor in biostatistics and meta-analysis.

-Marianna Boia-Ferreira is a pharmacist with PhD in Molecular and Cellular Biology and post doctorate (in progress) in Molecular and Cellular Biology. Research line on cell biology, molecular biology, experimental oncology, biochemistry, and toxicology. Professor of medical molecular and cellular biology.

- Francelise Bridi Cavassin is a pharmacologist, with PhD (in progress) in Internal Medicine. Research line on clinical-epidemiological studies, pathophysiological mechanisms and therapeutic strategies related to communicable and non-communicable diseases. Professor of medical pharmacology and study coordinator for clinical trials.