Review

Chemotherapeutic effects of Apigenin in breast cancer: Preclinical evidence and molecular mechanisms; enhanced bioavailability by nanoparticles

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ABSTRACT

This review highlights using nanotechnology in increasing the bioavailability of AP (Apigenin) to enhance its therapeutic efficacy in breast cancer treatment. Breast cancer is one of the most leading causes of cancer death in women both in developed and developing countries. According to several epidemiological and clinical trial studies that indicate progestin-stimulated breast cancer in post-menopausal women; it is necessary to determine compounds to suppress or attenuate the tumor-promoting effects of progestins in breast cells. For this purpose, using the natural anti-progestins, including AP compared with the chemical ones could be significantly effective due to the lack of toxicities and contradiction effects. However, AP is categorized as a Class II drug of Bio- pharmacological Classification System with low solubility in water which limited its therapeutic effects. Therefore, nanotechnology due to the presentation of remarkable properties has overcome this limitation through enhanced the solubility and bioavailability of AP. In this regard, various nanocarriers such as nanocrystals, micelles, liposomes, PLGA, etc., have highlighted the significantly increased bioavailability and therapeutic ef- ficacy of AP. Therefore, we will focus on the anticancer effects of AP in breast cancers, including involved mechanisms, the chemistry of AP and its bioavailability, finally different nanostructure systems to enhance the bioavailability of AP.

Abbreviations

- AP: Apigenin
- BAX: Bcl-2-associated X protein
- Bcl-2: B-cell lymphoma 2
- BCRP: Breast cancer resistance protein
- CAFs: Cancer-associated fibroblasts
- COX2: Cyclooxygenase-2
- CSCs: Cancer stem cells
- CXCL12: Chemokine (C-X-C motif) ligand 12
- CXCR4: C-X-C chemokine receptor 4
- ER: Estrogen receptor
- ERK 1: Extracellular signal-regulated kinase 1
- FASN: Fatty acid synthase
- GMCSF: Macrophage colony-stimulating factor
- HIF-1: Hypoxia-inducible factor-1
- HRE: Hypoxia response element
- LSP: Leukocyte sub-populations

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Different human studies have confirmed the anticancer effects of flavonoids like luteolin, myricetin, kaempferol, quercetin, and AP (AP) against lung [16], colorectal [17], and ovarian [18] cancers. A study in Italy on 2569 women with breast cancer showed an inverse association between 6 classes of flavones and breast cancer risk [19]. AP, 4', C15H10O5; 5,7- trihydroxyflavone, is one of the flavone subclasses with a molecular weight of 270.24 MW [20]. AP presents in plant-derived beverages, fruits, and vegetables like parsley and tea [20, 21]. AP has potent antioxidant and anti-inflammatory activities with low intrinsic toxicity, making it a cancer chemopreventive agent [20]. Various studies have applied AP against breast cancer. Li et al. [22] reported the AP potency in inhibiting the proliferation, migration, and stemness features of triple-negative breast cancer (TNBC), in vitro and in vivo. It has been found that AP attenuates YAP/TAZ activity, CTGF and CYR61 expression, and disrupts the YAP/TAZ-TEADs protein-protein interaction. Another study used AP for suppressing TNFα related metastasis in human breast cancer cells [23]. AP suppressed TNFα releasing of CCL2 chemotactic protein through blocking mRNA and protein synthesis of ILKβe and phosphorylated extracellular signal-regulated kinase 1 (ERK 1/2) suppression.

Furthermore, recent studies have expanded the AP applications in breast cancer-related research and revealed more involving parameters which are crucial in the promising treatments. Drug resistance is an important hindering factor in existing breast cancer treatments. This mechanism hinders the successful treatment of patients. A promising solution could be identified, including the usage of new adjuvants along with existing drugs. The advantages of dietary flavonoids like AP could be beneficial in this field and improve the treatment efficacy of drug-resistant breast cancers. In addition, most conventional studies on analyzing the effects of different drugs and natural ingredients have been conducted on traditional two-dimensional (2D) cell cultures. The 2D models show limitations in fully mimicking native human three-dimensional (3D) tissues. Similarly, these models are incapable of imitating the complex structure of tumors, resulting in limited in vivo treatment efficacy and translation into clinical applications. Several groups have been considering these issues and proposing more innovative treatment mechanisms. Sudhakaran et al. developed triple-negative breast cancer (TNBC) spheroids with high cellular uptake and showed that AP induced apoptosis and inhibited the growth of TNBC patient-derived organoids as a chemotherapeutic adjuvant [24]. They regarded AP as chemosensitizers and showed that AP sensitized spheroids allowed doxorubicin to trigger the caspase-9-mediated intrinsic apoptotic pathway and induce DNA damage. They also showed that AP regulates the expression of ABCG4 and ABCG2 drug efflux transporters and involves apoptosis by targeting hnrNPA2. Another similar study showed that AP and hesperidin intensified the cytotoxic effect of doxorubicin on MCF-7 breast cancer cells [25]. Another potential mechanism is resistance to endocrine therapies by hyperactivation of Akt in the estrogen receptor (ER) expressed breast cancer cells. Pham et al. showed that AP exerts an antiproliferative effect on the active form of the Akt protein in MCF-7 cells by inhibition of Akt/FOXM1 signaling pathway and inducing G2/M phase cell cycle arrest and apoptosis [26]. Shendge et al. isolated AP from Clerodendrum viscosum leaves and evaluated its anticancer activity in MCF-7 cells. They reported that AP shows selective cytotoxicity, intracellular ROS, and nuclear fragmentation, and dose-dependent apoptosis. They also examined the role of p53 in AP-induced apoptosis in cells. They reported AP induced p53 expression, and as a result activation of the caspase-cascade pathway, and cleavage of PARP [27].

This research aimed to critically review, the different molecular mechanisms of AP against breast cancer, including induction of apoptosis and cell cycle arrest, inhibition of fatty acid synthase, tumor angiogenesis, anti-invasive and metastasis properties, inhibition of drug resistance and YAP/TAZ activity, and finally, improving the immune effects substances that make them promising in breast cancer studies [13].
Table 1
Molecular targets of AP in breast cancer.

| Mechanism                                      | Cell Type                        | Animal model                                      | Outcome/Molecular targets                                                                 | Ref.   |
|------------------------------------------------|----------------------------------|---------------------------------------------------|------------------------------------------------------------------------------------------|--------|
| Induction of apoptosis and cell cycle arrest   | BT-474 cell (MPA)-dependent      | medroxy progesterone acetate (MPA)-dependent      | ↓ cell growth in a dose- and time-dependent                                               | (28,   |
|                                                | 7, 12-dimethylbenz(a)anthracene (DMBA)-dependent tumors | BT-474 xenograft tumors                          | ↑ sub-G0/G1 apoptotic population                                                         | 44-48) |
|                                                | SKBR3                            |                                                   | - caspase-dependent extrinsic apoptosis                                                   |        |
|                                                | MCF-7                            |                                                   | - the same efficiency in both ER+ and ER- breast cancer cells                             |        |
|                                                | MDA-MB-231                       |                                                   | - ↓ caspases-8, -3, and PARP                                                             |        |
|                                                | MDA-MB-468                       |                                                   | - ↑ p-STAT3, p-JAK1 and p-JAK2 (upstream kinase of STAT3)                                |        |
|                                                | MCF-7                            |                                                   | - ↓ STAT3 signaling pathway                                                              |        |
|                                                | MDA-MB-453                       |                                                   | - ↓ ROS                                                                                |        |
|                                                |                                   |                                                   | - ↓ DNA synthesis in a subcytotoxic dose                                                 |        |
|                                                |                                   |                                                   | - ↓ cyclin-dependent kinase                                                              |        |
|                                                |                                   |                                                   | - ↓ cyclin B-associated cdc2 activity                                                   |        |
|                                                |                                   |                                                   | - ↓ phosphorylation of serine/threonine kinase Akt (protein kinase B) in subcytotoxic concentration |        |
|                                                |                                   |                                                   | - ↓ Akt in dose-dependent                                                                |        |
|                                                |                                   |                                                   | - ↓ cyclooxygenase-2 (COX2)                                                             |        |
|                                                |                                   |                                                   | - "switching-off" the hormonal receptor of breast cancer cells                          |        |
|                                                |                                   |                                                   | - HER2/neu degradation                                                                   |        |
|                                                |                                   |                                                   | - ↓ release of cytochrome c                                                             |        |
|                                                |                                   |                                                   | - ↓ receptor tyrosine kinases                                                           |        |
|                                                |                                   |                                                   | - ↓ expression of growth factors                                                        |        |
|                                                |                                   |                                                   | - ↓ critical transcription factors                                                      |        |
|                                                |                                   |                                                   | - ↓ p-STAT3, p-JAK1 and p-JAK2 (upstream kinase of STAT3)                                |        |
|                                                |                                   |                                                   | - ↓ p53 activation                                                                       | (31,   |
|                                                |                                   |                                                   | - ↓ apoptosis through ↓ FASN enzyme                                                      | 32)    |
|                                                |                                   |                                                   | - ↓ aromatase enzyme,                                                                   | (33)]  |
|                                                |                                   |                                                   | - ↓ aromatase mRNA                                                                      |        |
|                                                |                                   | nude mice                                        | ↓ HIF-1α and VEGF in both hypoxic and normoxic situations                               | (37,   |
| Inhibition of tumor angiogenesis               | HER2+ breast cancer cells such as | human placental microsomes                      | ↓ HIF-1α binding to Hsp90                                                                | 44, 49 |
|                                                | SKBR3 and MCF-7 cells             |                                                   | ↓ phosphorylation of AKT                                                                 |        |
|                                                |                                   |                                                   | ↓ HIF-1α through AKT signaling                                                          |        |
|                                                |                                   |                                                   | ↓ VEGF through ↓ STAT3                                                                  |        |
|                                                |                                   |                                                   | ↓ progestin-dependent induction of VEGF                                                  |        |
|                                                |                                   |                                                   | mRNA and protein                                                                       |        |
|                                               | MCF7 cells and the antiestrogen-resistant sublines |                                                      | ↓ TGF-β and MMP by ↓ TAM/ TANs and Treg                                                |        |
|                                               | T47-D cells                       | nude mice                                        | ↓ HGF                                                                                 |        |
|                                               | BT-474                           |                                                   | ↓ IL-1α                                                                               |        |
|                                               |                                   |                                                   | ↓ IL-6                                                                                |        |
|                                               |                                   |                                                   | ↓ NFκB which lead to ↓ TGF-b and MMP by ↓ TAM/ TANs and Treg                           |        |
|                                               |                                   |                                                   | ↓ HGF                                                                                |        |
|                                               |                                   |                                                   | ↓ P53/Akt                                                                             |        |
|                                               |                                   |                                                   | ↓ CXCR4                                                                               |        |
|                                               |                                   |                                                   | having potential to ↓ VEGF-C, MMP-2/, MMP-9, and Cox-2                                   |        |
| Anti-invasive and metastasis                   | MDA-MB-231                       | MDA-MB-231-derived xenograft tumors               | ↓ TNFa                                                                                | (23,   |
|                                                | Efficient in both TNBC and receptor positive breast cancer cells |                                                      | ↓ CCL2 via ↓ IKKβ/ε and other LSP                                                      | 50,    |
|                                                |                                   |                                                   | ↓ phosphorylated ERK 1/ 2                                                               | 51)    |
|                                                |                                   |                                                   | ↓ GMCSF                                                                               |        |
|                                               |                                   |                                                   | ↓ IL-1α                                                                               |        |
| Inhibition of drug-resistance                  | MDA-MB-231                       |                                                   | ↓ BCRP-mediated efflux of mitoxantrone                                                   | (52-54) |
|                                                | Efficient in both TNBC and receptor positive breast cancer cells |                                                      | (continued on next page)                                                               |        |
response. The chemistry of AP and enhancing the bioavailability of AP via nanoparticles was discussed in depth.

2. Molecular mechanism of AP in breast cancer

So far, extensive investigations either in vitro or in vivo have been demonstrated the AP mechanisms in breast cancers, including induction of apoptosis and cell cycle arrest, inhibition of fatty acid synthase (FASN), aromatase inhibition, inhibition of tumor angiogenesis, anti-invasive and metastasis, inhibition of drug-resistance, inhibition of YAP/TAZ activity, improved the immune response. AP function as a chemo-preventive or chemotherapeutic agent in breast cancer has been highlighted in the majority of reported documents. Interestingly, the AP efficiency in most types of breast cancer, such as HER2 positive, ERα positive, ERβ positive, triple-negative breast cancer, and drug-resistant species has been reported. It was shown that exposure to high doses of phytoestrogens like AP had the same efficiency in both ER+ and ER-breast cancer cells [28]. High doses of AP (50 µM) lead to “switching-off” the hormonal receptor of breast cancer cells.

A summary of AP molecular targets is shown in Table 1 Induction of apoptosis and cell cycle arrest have been reported as the most important mechanism of AP in the suppression of breast cancer. Apoptosis is a programmed cell death causing the elimination of cells without releasing harmful substances into the surrounding area. Two core pathways are considered for apoptosis, including the intrinsic – mitochondrial pathway and extrinsic – death receptor pathway which are schematically shown in Fig. 1. Various studies on breast cancer in vitro or in vivo demonstrated the strong apoptotic effect of AP in a dose- and time-dependent approach through both apoptosis pathways, including extrinsic and intrinsic pathways. Moreover, according to several epidemiological and clinical trial studies that indicate progesterin-stimulated breast cancer in post-menopausal women [29, 30]; in vivo studies show that AP as the natural anti-progestin has the inhibitory effects on the (MPA)-dependent 7, 12-dimethylbenz (a) anthracene (DMBA)-dependent tumors through apoptosis, and cell proliferation inhibition.

Noticeably, it was also shown that a sub-cytotoxic dose of AP suppressed DNA synthesis in a panel of human breast cancer cell lines including MDA-MB-231, MBA-MB-468, MCF-7, and SK-BR-3. In other words, cell viability was not affected by AP at 30 µM concentrations, while the same ones resulted in a dramatic decrease in DNA synthesis at 24 and 72 h of all breast cancer cell lines treatment. This effect of AP which is not restricted to breast cancer cells indicates a common mechanism of action including suppression of cyclin-dependent kinase by p21cip1 and p27kip1 and blockade of cyclin B-associated cdck2 activity. Increased ROS generation and decreased phosphorylation of serine/threonine kinase Akt (protein kinase B) in the phosphatidylinositol 3-kinase pathway has been reported as the further AP mechanism at sub-cytotoxic concentrations.

AP as a multi-target compound suppressed the growth of cancer cells by blocking the receptor tyrosine kinases, reduced expression of growth factors, p53 activation, and inhibition of critical transcription factors [28]. AP can also activate apoptosis by preventing fatty acid synthase, a key lipogenic enzyme overexpressed in various human malignancies, including breast cancer [31, 32]. On the other hand, the aromatase enzyme, CYP19, plays a key role in the conversion of androgens to estrogens which express over 60% in breast cancers. Aromatase suppression by phytoestrogens, including AP not only performs at the aromatase enzyme level but also takes place at the gene expression level [33].

Moreover, according to recent clinical trials, treatment with the combination of estrogen and progesterin hormones resulted in increased breast cancer among postmenopausal women than therapy with estrogen alone or placebo [29, 34]. In this regard, it has been demonstrated that progesterins stimulate breast tumor progression through induction of VEGF which in turn triggers angiogenesis [35, 36]. Mafuvadze and et al., found that AP (50 or 100 µM) suppresses progesterin-dependent induction of VEGF mRNA and protein, and inhibits the PR (progesterone receptor) protein expression in T47-D cells. Moreover, progesterin-dependent VEGF secretion from BT-474 was blocked by AP. These results indicated that AP as a chemopreventive agent has significant potential in post-menopausal women treated with oral progesterins [37].

Worth mentioning that mortality of breast cancer is induced by aggressive metastasis in which AP through blockade of TNFα, IL-6, and chemokines play an essential role in the suppression of breast cancer development, invasion, and metastasis. Moreover, administration of flavonoids accompanied with cytotoxic agents, apart from MDR reversal could provide extra anticancer mechanisms by inhibiting multiple pathways that the tumor cells can survive. Therefore, needs to be

| Mechanism | Cell Type | Animal model | Outcome/Molecular targets | Ref.
|-----------|-----------|--------------|--------------------------|------|
| Inhibition of YAP/TAZ activity | TNBC cells | in vivo limited dilution assay | ↓ mRNA expression of MDR1, ↓ MRPs, ↓ P-gp expression, STAT3, ↓ p-STAT3, ↓ nuclear translocation of STAT3, ↓ STAT3 target genes: VEGF and MMP-9, ↓ EBr, ↓ AIB1, ↓ p38, ↓ protein kinase A, ↓ mitogen-activated protein kinase, ↓ AKT ↓ CTGF, ↓ CYR61, disrupt YAP/TAZ:TEAD interaction, ↓ TAZ expression ↓ PD-L1 upregulation induced by interferon (IFN)-Y ↓ STAT1 phosphorylation, ↓ interleukin-2 | (55) |
| Improved the immune response | triple-negative MDA-MB-468, HER2+ SK-BR-3, and 4T1 mouse mammary carcinoma cells, as well as human mammary epithelial cells | | ~ | (43) |
determined the potent and nontoxic BCRP inhibitors because of their potential clinical application to reverse MDR. In this regard, AP as a potential chemosensitizing agent showed strong BCRP-suppressing effects in various studies through several mechanisms (Table 1).

Furthermore, overexpression of YAP/TAZ resulted in various biological processes, including epithelial-mesenchymal transition (EMT), tumor metastasis, and tumorigenesis [38–42]. Li and et al., [22] indicated that proliferation and migration of TNBC cells were significantly prevented by AP. It has also been reported that AP suppressed stemness properties of TNBC cells in both in vitro and in vivo investigations. Interestingly, the function of AP as an immune system modulator specifically in breast cancer has also been investigated in recent years [43]. Coombs and et al., [43] found that AP suppressed the upregulation of PD-L1 induced by interferon (IFN)-ϒ in various breast cancer cell types. The mechanistic basis of downregulation IFN-ϒ-induced PD-L1 expression by AP in MDA-MB-468 and 4T1 cells has been illustrated in Fig. 1.

3. Chemistry of AP

AP, 4,5,7-trihydroxyglavone, is a compound based on flavonoid subgroup that has a skeleton of 2-phenylchromen-4-one (2-phenyl-1-
benzopyran-4-one) (Fig. 2). AP has a pale yellow color, and low solubility in alcohol, however, is fully soluble in DMSO. Working with AP is really hard and needed thermodynamically controlled conditions due to the instability at room temperature. AP occasionally happens in plants as aglycone; usually is established as a conformation of glycoside form. Some researchers even support the notion that free API is produced of postharvest degradation procedure [12, 56]. In nature, the public flavonoid feature is development of O-glycosides but other properties of flavones are the formation of C-glycosides recognized by a “carbon–carbon bond among the anomeric carbon of the sugar molecule and the C-6 or C-8 carbon of the flavone nucleus” [57]. In the various groups have recognized various acylated glycosides forms of API [58, 59]. In plants, API is in an extensive kind of forms of glycosides that existence and ratio are influenced through genetic background, environmental growth situation, development phase [60]. Furthermore in glycosylation, in several plants, API forms dimer molecules to form bioflavonoids and other diverse structural groups. The greatest studied API dimer of pharmacological importance is amentoflavone (3, 8-biAP) which is established in recognized medicinal herbs such as St John’s wort [61], ginko (Ginkgo biloba L.) [62], and spike mosses [63]. AP is synthesized in the cytoplasmic surface of the endoplasmic reticulum and the reaction is catalyzed through a class of enzymes [64]. The significant stage in the synthesis of flavonoids is the production of naringenin chalcone by condensation and then intramolecular cyclization of three malonyl-CoAs and Coumaroyl-CoAs through chalcone synthesis (CHS). Additional action through the stereospecific catalysis of chalcone isomerase (CHI) outcomes in the synthesis of naringenin. Lastly, naringenin works as the substrate in order to the flavone synthase I (FSI) which catalyzes the construction of the compound [65]. API is irregularly established in its free form, so its creation is typically followed through additional action through formation of methyltransferases, glycosyltransferases, and hydroxyl transferases which catalyze methylation and hydroxylation of API to form varied derivatives. It has been described that one operative manner of AP glucosides synthesis is via the glycosylation reaction by uridine diphosphate-glucosyltransferase YjIC, from Bacillus licheniformis DSM 13. Numerous approaches are also accessible in order to the synthesis of AP such as microwaves irradiation of ketoester as the starting material or commercially phloroglucinol. Extensive kinds of various synthetic API derivatives are also synthesized as pharmacologically active compounds [66–69].

4. Increase bioavailability of AP

Based on the literature, there are several methods to increase the bioavailability of AP in different forms and concentrations, for different types of applications. Based on the biopharmaceutics classification systems, AP is a class II drug with considerable intestinal membrane permeability and also has very poor solubility in green media, especially water [70, 71]. There is wide interest in improving the bioavailability of AP via cross-linking them with biocompatible linkers, and also modifying the chemical structure with reactive functional groups; however, the most important factor in the improving of AP bioavailability, generally any compound, is considering the factors that may play a role in the mass production or entry of these compounds into the clinical phase [72, 73]. In this manner, Rabiee’s Theory (Variable Laws) [74] would be considered as a promising point. Rabiee’s theory is as follow:

![Fig. 3. Effect of NPs formulation on bioavailability of drugs. Reprinted with permission from the Elsevier [85].](image-url)
### Table 2
Summary of report on the production of AP-based NPs, particle size and their importance in increasing bioavailability. Keys: Carbon nanopowders: CNPs; AP-phospholipid phytosome: APLC.

| Types of nanomaterials | Production techniques used | Particle size (nm) | Bioavailability improved | Drug delivery | Type of study | Year | Ref |
|------------------------|----------------------------|-------------------|--------------------------|---------------|--------------|------|-----|
| AP nanocrystals        | Supercritical antisolvent process | 400–800          | 3.4-fold                 | Oral          | In vitro     | 2013 | [94]|
| AP-loaded polymeric micelles | Spray drying technique | –                | 2.5-fold                 | Oral          | In vitro, in vivo (Male Wister Albino rats) | 2018 | [95]|
| AP-loaded mixed micelles APLC | Ethanol thin-film hydration method | 178              | 4.03-fold               | Oral          | In vitro, in vivo (Male Sprague-Dawley rats) | 2017 | [78]|
| AP NPs                 | Liquid antisolvent precipitation technique | 159              | 4.96-fold               | Oral          | In vitro     | 2017 | [97]|
| AP liposomes           | lipid film hydration       | 103              | –                       | Vein          | In vitro, in vivo (Athymic nude mice (mu/m, 4-6 week)) | 2017 | [87]|
| Mesoporous silica      | physical absorption        | 49               | Enhanced bioavailability | Oral          | In vitro, in vivo (female Sprague-Dawley rats) | 2019 | [86]|
| CNPs                   | Solvent evaporation        | 40               | Increased bioavailability of AP by approximately 183% | Oral          | In vitro, in vivo (Male Sprague-Dawley rats) | 2014 | [98]|
| AP-PGLA                | Multiple emulsion solvent evaporation | 226              | Enhanced bioavailability | Intraperitoneal | In vitro, in vivo (Swiss albino mice) | 2018 | [99]|

\[ V_h + V_b \propto V_{total}\]

The number of biomaterials (Vb) and host variables (Vh) depends on a variety of factors, and by increasing the number of biomaterials and host variables, the amount of total variables also increases and as a result, performance and, consequently, biomaterial behavior in the host environment will have less control and predictive capabilities. For an external substance that is supposed to be in the human body, it must be predictable and controllable. In addition, according to the principle that the host in an individual does not have the ability to change, therefore, by using the simpler biomaterials (with fewer variables), the above goal is more accessible.

The biocompatibility examinations in order to a biomaterial based on obtainable protocols and standards, the appropriate compatibility (AC) parameter is also needed in agreement with Rabiee’s theory. The summary of this theory and relationship is as follows:

\[ AC \propto V_{ab} \]

\[ AC \propto V_{sh} \]

\[ AC \propto V_{ab} \times V_{sh} \]

\[ AC = \alpha \times V_{ab} \times V_{sh} \]

In the above equations, \( V_{ab} \) is the amount of variation numbers of biomaterials and \( V_{sh} \) is the amount of variation numbers of the host. In general, the host is not controllable, and it varies in individual numbers and any part, therefore, we assume the amount of variation numbers of the host (\( V_{sh} \)) is 100. \( \alpha \) is the biomaterial constant that depends on the component’s variations (\( V_c \)) and the morphology simplicity variation (\( V_{ms} \)), therefore, the final equation is:

\[ AC = 100 \times \alpha \times V_{ab} \]

In the case of AP bioavailability, the correct logic is that based on the above mentioned, it should improve the bioavailability of the AP at the lowest cost as well as maximum efficiency by a simple, tunable and fully accessible protocol. There are limited articles that emphasize improving the bioavailability of AP by the mentioned protocol, but encapsulating the AP into biocompatible, biodegradable and low-cost polymers is the desired protocol [75–78].

### 5. Enhanced bioavailability of AP via nanoparticles

Nanomaterials/nanoparticles (NP) consider as emerging materials in medicine with application from drugs, genes and other medical fields [79]. Examples are recent COVID-19 vaccines from both Pfizer’s and Moderna’s contain mRNA wrapped in lipid nanoparticles (LNPs) that support carrying it to human cells nevertheless also act as an adjuvant, a vaccine ingredient that bolsters the immune response [80]. The nanoparticles are <100 nm in size, and a wide range of drugs, including hydrophilic and hydrophobic small drugs, flavonoids, vaccines and biological molecules, can be delivered by these NPs [81–83]. Application of NPs in drug delivery can be mentioned in diseases such as cancer, cardiovascular and Alzheimer’s disease [84]. The NPs help improve several features to attain improved bioavailability, as shown in Fig. 3 [85].

AP acts well in pharmacological aspect, but due to its poor solubility, its clinical application has been limited. Therefore, new formulations or methods should be developed to improve solubility of AP and its bioavailability [86]. Numerous kinds of nanomaterials such as metallic-based nanomaterials, lipid-based and polymeric nanoparticles were developed in order to the highly effective delivery of AP [86–88]. The oral bioavailability of AP nanoparticles was about 5 fold upper compared to the naked AP, and this formulation shows no toxic outcome on the organs of mice [89]. Various studies have revealed that solid dispersion (SD) can be effectively applied in order to the improving the dissolution level of poorly water-soluble drugs [90]. Metallic nanoparticles and carbon-based nanomaterials have been broadly applied as drug delivery systems, predominantly in targeted therapy [91]. Lipid-based nanocarriers are applied to progress the high-efficiency delivery and bioavailability of AP. Furthermore, the appliances of lipid-based nanoparticles to overcome the MDR have been proposed based on improved permeability of membrane [92, 93]. Examples of applications of NPs in the delivery of AP have been shown in Table 2. It demonstrated that NPs significantly improve solubility and bioavailability of AP in vitro and preclinical animal models.

Solid dispersion (SD) is an extensively applied method to improve dissolution of poorly water-soluble drugs [100]. Carbon nano powders (CNPs) are carbon nanomaterials with less than 100 nm, can be used as nanocarriers for SD preparation and to increase drug solubility. These materials have properties such as large specific surface area and high dispersibility, which reduces drug particle size and improved SD. For preclinical research, oral administration of AP resulted in low blood levels, with a Cmax of 1.33 μg/mL and AUC 0–t of 11.76 μg h/mL. With CNPs drug nanomaterial of SD, the oral bioavailability of AP was increased by approximately 183% [98].

Mesoporous silica NPs (MSNs) are insoluble nanomaterials, so these carriers can be classified into the last generation SD. These particles
have many advantages such as high biocompatibility and biodegradability, pore size with narrow distribution, and stability [101]. As a result, MSNs are a good choice in order to drug delivery according to their exclusive properties and low toxicity. In a study, MSN showed increased solubility and oral bioavailability of AP. AP-MSN was prepared by physical absorption, and the AP-MSN SD was synthesized at the weight ratio of 1:1 to get the high solubility. As a result, this solubility of AP-MSN SD was larger than AP. The results of the study showed that the concentration of AP is usually very low, but oral bioavailability of AP-MSN SD enhanced by 8.32 times than AP in 2.5–8 h. So, AP-MSN SD has a good outlook to be applied as new oral formulation for clinical application [102].

Various methodologies have been used to enhance the AP dispersion (SD) and improve its bioavailability. Spray drying technique was established to increase the bioavailability of AP by formation of AP-loaded Pluronic F-127 (PL-F127) polymeric micelle (95). PLF-127 is a non-ionic amphiphilic copolymer comprised of ethylene oxide (PEO) and propylene oxide. At high copolymer concentrations, micelles are packed leading to gel-like performance. These polymers can be widely used in increasing solubility and bioavailability of different molecules [103, 104]. Mixed micelles system act as an effective drug delivery system, which has the capability to control the drug’s release, due to its core-shell structure, and can also improve the solubility of hydrophobic drugs. An AP-loaded mixed micelles (AP-M) system comprising two copolymers of soluplus and PL-F127 polymers with size 178.5 nm, prepared by ethanol thin-film hydration method. This system has been helping to improve oral bioavailability (more than 4-fold), and increase water solubility, high Caco-2 cellular uptake and gastrointestinal absorption of AP than free AP in rats [78]. Poly lactic co-glycolic acid (PLGA), as polymeric NPs, have unique properties such as nontoxic and biodegradable, and are highly popular as nanocarrier. These NPs have been approved by the Food and Drug Administration (FDA) in US as an intravenous drug delivery system [105, 106].

Evaluation of human hepatocellular carcinoma cell line such as HepG2 and Huh-7, after administration of AP-loaded NPs (20 mg/kg body weight per week) in rats, showing reduced nodule size, number, and area liver lesions after apigenin treatment. These NPs were more effective for the inhibition of tumor growth, associated with a sustained release of AP-loaded NPs than the free form. This formulation of AP improved its bioavailability and made it more tumor site specific in nature [107]. PLGA NPs can reduce cancer cell survival without damaging healthy cells.

The PLGA-based nanoformulation containing aptamer-conjugated AP-loaded PLGA NPs with average size of 226 nm, was found to have anti proliferative action both in vitro and in vivo colorectal cancer model as shown in Fig. 4. These nanocarriers were effectively delivered AP to the targeted region. This nanoplatform accumulated in the colon, which increases therapeutic efficacy to colorectal cancer cells and decreases off-target cytotoxicity. The outcome was AP bioavailability in colorectal tissue and plasma increased significantly after AP-ANP treatment, with low levels of toxicities [99]. The recent development of graphene and its derivatives are emerging as effective gene/drug delivery system. Functionalized graphene oxides (FGO) are nontoxic, biocompatible and have properties including strong, light and conductive. A recent study of paclitaxel with FGO-AP produces synergistic effects in human ovarian cancer cells via the modulation of anti-apoptotic

Fig. 4. Schematic illustration of the efficacy of HCT-116 cell-targeted aptamer-conjugated AP-loaded PLGA NPs, followed by in vivo efficacy in a mouse model of colorectal cancer. Reprinted with permission from the American Chemical Society [99].
the delivery of poorly water-soluble drugs [96]. Phospholipids that can increase the overall bioavailability and solubility of drugs can take the AP to enter the nucleus of the cells and cause higher mitochondrial apoptosis and reduced side effects of paclitaxel chemotherapy [108].

Examples of this work are carried out on AP-phospholipid phytosome (APLC) to increase the drug's solubility, antioxidant activity, and in vivo oral bioavailability. APLC enhances the aqueous solubility of AP in water by 37-fold (22 µg/mL) compared with AP (0.62 µg/mL). It establishes that phytosome is a capable formulation approach for increasing the delivery of poorly water-soluble drugs [96].

The role of AP as a protective agent in IR-induced acute kidney injury (AKI) was developed. Intraperitoneal injection of AP at specific doses (5, 10, and 20 mg/kg) was performed on mice. Loading of AP in degradable polymer nanoparticles can increase its bioavailability. AP reduces inflammation by silencing the NF-B pathway through increasing miR-140–5p expression and decreasing expression in CXCL12 in vivo and in vitro. As a result, it can act as a therapeutic agent in patients with IR-related kidney injury [110].

There are lots of NPs and lipid-based carrier systems such as phospholipids that can increase the overall bioavailability and solubility of some compounds, like curcumin, chrysophanol, and naringenin with plenty in vitro and early phase of the preclinical trial on a rodent model.

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Table 3 A list of AP clinical trials studies.

| Studies                      | Trial ID      | Mechanism of action                                                                 | Clinical Phases/Study design |
|------------------------------|---------------|-------------------------------------------------------------------------------------|------------------------------|
| Chemotherapy-induced Oral Mucositis | NCT04317183  | Topical chamomile oral gel may affect the prevention of chemotherapy-induced oral mucositis | Recruiting/Phase 2           |
| Diabetes Mellitus Type 2     | NCT04233658  | Chlorogenic acid, luteolin and AP can be improved antioxidant effects through downregulation of glaucomaens. | Phase 3                     |
| Pancreatic Cancer            | NCT00609310  | The effect of AP on GLUT-1, HIF and VEGF prevents the proliferation of PC cells       | Recruiting/Phase 2           |
| COVID                        | NCT04404218  | The use of natural extracts such as AP to diminish inflammation in patients with SARS-COV-2 | Recruiting/Phase 2           |
| Cardiovascular Risk (NUT)    | NCT04114916  | Changes in the dilatation of the Humeral artery                                      | Completed                    |
| Allergic Rhino Conjunctivitis| NCT00365648  | The use of rosmarinic acid, AP, luteolin and chrysosorol can prevent the release of histamine and interleukins | Completed                    |

Biotechnology Reports 34 (2022) e00730

However, these materials also suffer from challenges of drug discovery, have played a major role in pharmacotherapy, including cancer diseases. However, these materials also suffer from challenges of drug discovery, like screening, isolation, characterization and optimization. Recently, various scientific and technological advances, containing genome nanoparticles. The liposome is made of nanobubble (vesicle), it is the same material as a cell membrane. It can be filled with drugs and then deliver to target cells. It is an excellent drug delivery vehicle, transporting a cargo of interest within a protective, outer layer of lipids. In fact, they are an innovative drug delivery system; and comprising of bilayers that form extemporaneously when phospholipids are dispersed in water [111]. Liposomes are generally used in the form of several commercial products, including α-alpha-tocopherol polyethylene glycol succinate (TPGS), which is a water-soluble solution derived from esterified polyethylene glycol, vitamin E succinate, and is used as a nanocarrier. Promoting the bioavailability of anticancer drugs and inhibiting the resistance of several drugs are the benefits of this nanocarrier [112]. The combination of AP -TPGS and Tyroservatide (YSV), which showed important anti-tumor effects against A549 cancer cells [113].

The application of liposome with capsulation AP, with nano size of 103 nm, tested in vitro cells work with CRC cell lines HT-29. The experimental results confirmed liposome-AP improved cytotoxicity and the bioavailability of AP. The results also showed that low hemolysis caused by liposomes made their hemocompatibility and made them suitable for intravenous injection [87]. Encapsulated AP with SLNP exhibited improved effectiveness in the treatment of diabetes mellitus. This highly bioavailable AP-SLNP with the size of about 150 nm, cab be enhanced HO-1 and Nr2 expression and decreased the NF-kB activity, leads a protective effect against diabetic properties by anti-inflammatory and anti-oxidant activity, as well as reduced level of glucose in the blood in rats [114]. However, Lipid-based carriers have been shown to be suitable as oral delivery vehicles, but, high lipolysis of lipid-based carriers in the gastrointestinal tract reduces their lifespan in the circulation [87, 115]. Moreover, studies have shown that lipid-reconstitution after lipolysis in vivo using non-water-quenching dye. The encapsulated in the lipid-based carrier can be monitored the reconstitution of lipolytic products offers record for the gastrointestinal tract condition of lipid-based nanocarriers [116, 117]. Table 3 shows a list of some clinical trials used for Apigenin in various interventions in the https://clinicaltrials.gov/ site.

6. Conclusion and future prospective

Breast cancer is the second leading cause of death from cancer in women worldwide. Moreover, one of the breast cancer subtypes, TNBC has attracted a wide scientific and clinical attentions because of its heterogeneity, poor prognosis, and lack of the targeted therapy strategies. Based on several studies, the risk of this subtype as a heterogeneous disease varies in different western and Asian populations. The differences are related to its prevalence, while the risk factors and treatment options are in common [118]. Surgery, radiation and chemotherapy are some of the treatments that can be used for breast cancer. However, it is important to find and develop chemo-preventive factors to prevent and / or manage the breast cancer. A wide variety of epidemiological and experimental researches showed the efficacy of dietary phytochemicals in breast cancer prevention [119].

The above discussed literature emphasized the anticancer potential of apigenin. It was demonstrated that apigenin as a potent agent suppress almost all types of breast cancer. Nevertheless, the most findings are resulted from in vitro studies which cannot be extended the dosage and efficacy to living systems because of their various enzymes and immune system, leading apigenin degradation and regulation the pathways respectively. Albeit, some in vivo studies have also demonstrated cancer-preventing properties of apigenin, but unfortunately, the studied variable numbers are restricted [120].

Since ancient times, natural products (NPs) and their derivatives have played a major role in pharmacotherapy, including cancer diseases. However, these materials also suffer from challenges of drug discovery, like screening, isolation, characterization and optimization. Recently, various scientific and technological advances, containing genome
mining and engineering approaches, and analytical tools improvement, and microbial culturing developments consider these challenges and create the novel opportunities. Therefore, using the natural products in pharmaceutical therapy, especially for circumvent antimicrobial resistance is revived [121].

The dietary-derived natural materials have been traditionally used for the prevention and treatment of cancers, and many new synthetic drugs are the extract of these materials. Hence further research should be carried out on the effectiveness of these materials for the treatment of cancer. In the last decades, various research studies have confirmed the multiple anticancer effects of flavonoids, especially their subclass, AP. Different molecular mechanisms against breast cancer make AP a promising potential for breast cancer prevention and treatment. AP has different physicochemical and biological properties that are essential in cancer treatment. The AP can be stable and reactive; however, it can interact in different stages of breast cancer development and active enzymes and molecules. In this regard, the chemistry of AP, the main molecular mechanisms of AP against breast cancer, and the different methods to improve its bioavailability were discussed. Among different approaches of bioavailability enhancing, NPs can enhance the delivery and interaction of AP into cancer cells. The mechanisms of enhancing the bioavailability of AP via NPs were discussed in detail. It has been demonstrated that conjugation or encapsulation of AP with NPs, can enhance the solubility, biodegradation, bioavailability, and absorption of AP, leading to better chemo-preventive and chemotherapeutic efficacy. In this regard, different NPs, their synthesis methods and the mechanism of enhancing bioavailability were reported.

AP has been introduced as an anticancer agent. However, further studies are required to fully understand its mechanism of action on cancer cells and tumors in a clinical setting. The exact mechanism should be investigated in therapeutic effects against every specific cancer cell, the interactions among the involved mechanisms, and modulating them. Any further study will complete the existing data and can optimize the therapeutic effects of AP. In addition, their synergistic anticancer effects with NPs and cell-specific delivery by nanomedicine through targeting approaches can be studied in future researches. More in vivo results and clinical data of these AP-nanomedicine systems can help to fight against breast cancer.

**Author contributions**

AM performed different analyses. All authors helped in performing and drafting the manuscript. The authors read and approved the final manuscript.

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**Competing Interests**

The authors declare that they have no competing interests.

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Biotechnology Reports 34 (2022) e00730
