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1	Natural products targeting macrophages in tumor
2	microenvironment are a source of potential antitumor agents
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21 ABSTRACT

Background: Macrophages are one of the major cell types in the immune system and 22 are closely related to tumor development, which can be polarized into M1 type with 23 anti-tumor activity or M2 type with pro-tumor activity. The infiltration of more 24 macrophages into tumor predicts poorer prognosis due to their more exhibition of M2 25 phenotype under the influence of many factors in the tumor microenvironment (TME). 26 Therefore, reverse of M2 macrophage polarization in TME is conducive to the 27 suppression of tumor deterioration and understanding the influencing factors of 28 29 macrophage polarization is helpful to provide new ideas for the subsequent targeting macrophages for tumor therapy. 30

Purpose: This review summarizes the effects of TME on macrophage polarization and
 natural products against M2 macrophage polarization, which may provide some
 directions for tumor therapy.

Methods: The search of relevant literature was conducted using the PubMed, Science
Direct, CNKI and Web of Science databases with the search terms "macrophage",
"tumor microenvironment", "natural product" and "tumor".

Results: The mutual transformation of M1 and M2 phenotypes in macrophages is influenced by many factors. Tumor cells affect the polarization of macrophages by regulating the expression of genes and proteins and the secretion of cytokines. The expression of some genes or proteins in macrophages is also related to their own polarization. Many natural products can reverse M2 polarization of macrophages which 42 has been summarized in this review.

43 *Conclusion:* Regulation of macrophage polarization in TME can inhibit tumor
44 development, and natural products have the potential to impede tumor development by
45 regulating macrophage polarization.

46 Key words: Natural product; Macrophage; Polarization; Tumor microenvironment;
47 Immune

Abbreviations: AIE, Aggregation-induced emission; ALOX5AP, Arachidonate 5-48 Lipoxygenase activating protein; ARCR, Astragalus mongholicus Bunge-Curcuma 49 aromatica Salisb. extract; ASO, Antisense oligo nucleotide; CAFs, Cancer-associated 50 fibroblasts; CTHRC1, Collagen triple helix repeat containing 1; C5aR, Complement 5a 51 receptor; DCLK1, Doublecortin-like kinase 1; DC-SIGN, DC-specific ICAM-3-52 grabbing non-integrin; DHA, Dihydroartemisinin; DLBCL, Diffuse large B-cell 53 lymphoma; EAT, Ethyl acetate fraction of Adenophoratriphyllavar.japonica; ESCC, 54 Esophageal squamous cell carcinoma; FGL2, Fibrinogen-like protein 2; FoxQ1, 55 Forkhead box Q1; GBC, Gallbladder cancer; GBM, Glioblastoma multiforme; GLSP, 56 G. lucidum spore polysaccharide; Gpr132, G protein-coupled receptor 132; HNSCC, 57 Head and neck squamous cell carcinoma; HMGA2, High-mobility gene group A2; HPV, 58 Human papilloma virus; ICAM-1, Intercellular cell adhesion molecule-1; IL-10, 59 Interleukin-10; IFN-y, Interferon gamma; IL1RL10, Interleukin-1 receptor like 1; 60 ISG15, Interferon-stimulated gene 15; NF-KB, Nuclear factor kappa-B; NPC, 61 62 Nasopharyngeal carcinoma; NSCLC, Non-small cell lung cancer; MEMA, Methylene chloride extract of Morus alba L; MK2, MAPK-activated protein kinase 2; MIF, 63

64	Migration inhibitory factor; MMP, Matrix metalloproteinases; MMR, Macrophage
65	mannose receptor; M-CSF, macrophage colony-stimulating factor; ObR, leptin receptor;
66	PAI-1, Plasminogen activator inhibitor-1; PINK1, PTEN-induced kinase 1; PTX,
67	Paclitaxel; PDA, Pancreatic ductal adenocarcinoma; PGE2, Prostaglandin E2; PTEN,
68	Phosphatase and tensin homolog deleted on chromosome 10; PPARc, Peroxisome
69	proliferator-activated receptor-c; Prxs, Peroxiredoxins; RKIP, Raf kinase inhibitory
70	protein; ROS, Reactive oxygen species; SI-CLP, Stabilin-1 interacting chitinase-like
71	protein; SLC2A, Solute carrier 2A; SMS2, Sphingomyelin synthase 2; SPON2,
72	Spondin-2; SUCNR1, Succinic acid receptor; STAT, Signal transducer and activator of
73	transcription; SYK, Spleen tyrosine kinase; S100A9, S100 calcium-binding protein A9;
74	TAMs, Tumor-associated macrophages; TDO2, Tryptophan 2,3-dioxygnease 2; TFEB,
75	Transcription factor EB; TGF- β , Transforming growth factor- β ; TME, Tumor
76	microenvironment; TLR7, Toll-like receptor 7; TNBC, Triple-negativebreast cancer;
77	TNFSF15, Tumor necrosis factor superfamily-15; VEGF, Vascular endothelial growth
78	factor; YPF, Yu-Ping-Feng

80 Introduction

Tumor microenvironment (TME) plays an important role in tumor metastasis, 81 immunosuppression and chemotherapy resistance, which mainly includes tumor cells, 82 infiltrating immune cells (macrophages, lymphocytes, dendritic cells, etc.) and 83 infiltrating stromal cells (cancer-associated fibroblasts, endothelial cells, etc.) (Kenny 84 et al., 2007; Mao et al., 2021). Macrophages as the most widely infiltrating immune 85 cells in TME provide support for the development of tumors(Qian and Pollard, 2010). 86 Tumor-associated macrophages (TAMs) recruit endothelial cells by secreting a variety 87 of cytokines such as vascular endothelial growth factor (VEGF) and matrix 88 metalloproteinases (MMP), thereby inducing angiogenesis in tumor sites which is the 89 main reason for tumor growth and invasion(Cendrowicz et al., 2021). TAMs also inhibit 90 91 the cytotoxic activity of T lymphocytes and NK cells by releasing immunoregulatory factors such as prostaglandin E2 (PGE2), interleukin-10 (IL-10) and transforming 92 growth factor- β (TGF- β) to exert immunosuppressive effect(Li et al., 2011), indicating 93 that TAMs are a potential target for tumor therapy. Plasticity is one of the key features 94 of macrophages, which can make their phenotypes and functions adapt to the needs of 95 the surrounding environment to promote tumor deterioration. 96

97 As shown in Figure 1, macrophages can be divided into classically activated
98 macrophages (M1 type) and alternatively activated macrophages (M2 type)(Liu and
99 Wang, 2020). Interferon gamma (IFN-γ) induces the polarization of macrophages into
100 M1, promoting T helper (Th) 1 immune response and anti-tumor activity(Locati et al.,

2013), while IL-4/IL-13 elicits their polarization into M2, increasing anti-inflammatory
Th2 immune response and pro-tumor activity. In addition, M2 macrophages can be
further subdivided into M2a, M2b, M2c and M2d under different stimuli. M2a and M2b
play an immune regulatory role and drive Th2 response, while M2c plays a leading role
in inhibiting immune response and promoting tissue remodeling. M2d, also known as
tumor associated macrophages (TAMs), is closely associated with tumor progression(Li
et al., 2011).

Macrophages are one of the main immune cells in the immune system, which can 108 109 regulate homeostasis, resist pathogens and promote wound healing(Wang et al., 2021a). In TME, most macrophages show M2 phenotype with tumor promoting effects due to 110 the influence of the surrounding environment. Nevertheless, a small number of 111 112 macrophages still display M1 phenotype with anti-tumor ability. Therefore, understanding the regulatory factors related to the differentiation and function of 113 macrophages is conducive to the development of drugs targeting macrophages further. 114 115 This review summarizes the regulatory mechanism of macrophage polarization in TME and natural products against M2 polarization, so as to provide directions for tumor 116 therapy. 117

Tumor microenvironment facilitates polarization and recruitment of macrophages

120 *Regulation of macrophage polarization and recruitment*

Macrophages exhibit different phenotypes due to the influence of surrounding 121 environment, which is related to the expression of proteins or genes in macrophages. 122 Therefore, the effects of genes or proteins in macrophages on their functions are 123 summarized below to provide some idea for regulating macrophages in TME. It is well 124 known that TAMs exhibit various functions in TME, such as promoting angiogenesis, 125 mediating immune escape and accelerating tumor cell migration. In addition, TAMs 126 still maintain phagocytic function and present anti-tumor activity under appropriate re-127 education which is regulated by protein or gene in macrophages (Lecoultre et al., 2020). 128 VentX, a master regulator of macrophage plasticity is associated with the phagocytic 129 activity of macrophages, which is significantly decreased in TAMs in the pancreatic 130 ductal adenocarcinoma (PDA) microenvironment. The recovery of VentX expression 131 in TAMs promotes phagocytosis, but the mechanism remains unclear(Le et al., 2020). 132 The metabolism is also related to macrophage phenotypes and functions(Zhang et al., 133 2021a). As mentioned above, macrophages can exhibit M1 and M2 phenotypes, which 134 have different metabolic patterns due to their different functions. M1 macrophages are 135 characterized by aerobic glycolysis, while M2 by oxidative phosphorylation. IL-33/ST2 136 axis was reported to be associated with oxidative phosphorylation and glycolysis in 137 macrophages, which enhances mitophagy through the activation of mTOR and then 138

139	increase the expression of genes related to M2 polarization, promoting M2 polarization
140	further (Xu et al., 2021b). Integrin is a cell adhesion and signal protein which plays an
141	important role in the biological function of cells(Slack et al., 2022). The overexpression
142	of integrin β 3 on the surface of TAMs <i>in vivo</i> and <i>in vitro</i> accelerates M2 polarization
143	through activating peroxisome proliferator-activated receptor-c (PPARc)(Shu et al.,
144	2020). Collagen triple helix repeat containing 1 (CTHRC1), a secreted ECM protein,
145	promotes the recruitment of TAMs through integrin β 3/PI3K/Akt/CX3CR1 signaling
146	pathway(Li et al., 2019) and promotes M2 polarization through the activation of
147	pSTAT6(Bai et al., 2020). SPON2 in macrophages activates RhoA and Rac1 by acting
148	on $\alpha 4\beta 1$ integrin, promotes F-actin reorganization and further increases M1-like
149	macrophage recruitment(Zhang et al., 2018b). However, SPON2 has been reported to
150	be associated with a poor prognosis in colorectal cancer and promote macrophage M2
151	polarization through activating integrin β 1/PYK2 axis(Huang et al., 2021a). ROS is
152	involved in a plethora of processes in cells and plays an important role in macrophage-
153	mediated immunity(Herb and Schramm, 2021). Isoprenaline facilitates the M2
154	polarization of breast cancer macrophages through inhibiting autophagy probably by
155	regulation of ROS/ERK and mTOR signaling pathways, indicating that repression of
156	autophagy may be a possible treatment for cancer (Shan et al., 2017). M2 macrophages
157	modulated the secretion of IL-1 β by regulating fatty acid oxidation in ROS and NLRP3
158	dependent manner, thus promoting the development of cancer(Zhang et al., 2018a).
159	Peroxiredoxins (Prxs) are a family of antioxidant enzymes that possess the ability of
160	removing H ₂ O ₂ and peroxynitrite. When the lung carcinoma cells with or without

161 knockdown of Prx5 are injected to WT or Prx5-/- mice, the volume of the tumor is
162 related to the expression of Prx5 in the mice and but not in the cancer cells injected,
163 indicating that tumor growth is uncorrelated with the expression of Prx5 in tumor cells.
164 The deficiency of Prx5 in macrophages induces ROS accumulation, promoting their
165 own M2-like phenotype (Seong et al., 2021).

Cytokines promote tumor development and interleukin-10 (IL-10) is known as an 166 anti-inflammatory and immunomodulatory cytokine which has been proved to suppress 167 inflammatory response through inhibiting the activation of macrophages(Kim et al., 168 169 2020). The expression and secretion of IL-10 in TAMs are closely related to their functions. OVOL2 expression is higher in M1 macrophages than in M2. The 170 overexpression of OVOL2 decreases M2 polarization of macrophages by inhibiting the 171 172 transcription of IL-10(Wu et al., 2022). The overexpression of nuclear factor of activated T cells 1 (NFATc1) in macrophages is associated with tumor growth. The 173 tumor volume in mice subcutaneously inoculated with sh-NFATc1 TAM + SiHa is 174 175 lower than that with shNC TAM + SiHa, revealing the important role of NFATc1 in the tumor growth. Mechanically, the overexpression of NFATc1 in macrophages facilitates 176 M2 polarization by regulating c-myc/PKM2 pathway to enhance IL-10 secretion(Tan 177 et al., 2022). Chemokines are chemotactic cytokines which can cause the targeted 178 migration of leukocytes. Most cells in TME secrete a series of chemokines that affect 179 TME by recruiting stromal cells and stimulating angiogenesis(Balkwill, 2004). 180 According to the number and spacing of the first two cysteine residues in the amino-181 terminal part of the protein, chemokines are divided into four groups, i.e. C, CC, CXC 182

and CX3C(Slettenaar and Wilson, 2006). Macrophages in TME can recruit more from 183 other sites and induce their polarization by secreting chemokines. PTEN (phosphatase 184 and tensin homolog deleted on chromosome 10) is regarded as a new tumor suppressor 185 regulated by NHERF-1, whose deficiency drives M2-like polarization of macrophages 186 in TME by increasing CCL2 and VEGF-A (Li et al., 2015). CCL2 and IL-6 recruit 187 monocytes to TME and increases their polarization into M2 macrophages by inhibiting 188 caspase-8 cleavage and enhancing autophagy in macrophages(Roca et al., 2009). S100 189 calcium-binding protein A9 (S100A9) is an inflammatory microenvironment-related 190 191 secretory protein up-regulated in TAMs and acts on tumor cells through AGER/NF-KB axis, thereby facilitating the transcription of CCL2, which accelerates the expression of 192 S100A9 in macrophages in return(Wei et al., 2021). The deficiency of MAPK-activated 193 194 protein kinase 2 (MK2) in macrophages inhibits tumor angiogenesis by regulating the secretion of CXCL-12/SDF-1, suggesting that MK2 inhibitor may be a potential 195 treatment for cancer(Suarez-Lopez et al., 2020). Chemokine receptors also play an 196 197 important role in the polarization of macrophages. The up-regulation of CX3CR1 in TAMs is related to the poor prognosis of cancer. The knockout of CX3CR1inhibits 198 tumor angiogenesis and liver metastasis in mice and the mechanism needs further 199 investigation (Zheng et al., 2013). 200

The aberrant expression of proteins or genes in macrophages can induce macrophage polarization to promote their recruitment from other sites. Therefore, understanding the proteins or genes related to the polarization and function of macrophages is instrumental in provide an idea for the subsequent therapy targeting 205 macrophages. The regulation of polarization and recruitment of macrophages is shown206 in Table 1.

207 Effects of tumor cells on polarization of macrophages

Macrophages can exhibit specific phenotypes when affected by the surrounding 208 environment. The communication between tumor cells and macrophages in TME 209 plays a key role in mediating the function of macrophages. Signals from tumor cells 210 can induce the additional functions of macrophages(Jiang et al., 2021; Pan et al., 2020). 211 Ovarian cancer stem cells promote macrophage M2 polarization by activating the 212 PPARγ and inhibiting NF-κB pathway(Deng et al., 2015). The M2 polarization and 213 PD-L1 expression of macrophages are also facilitated by hemangiosarcoma 214 cells(Gulay et al., 2022). Exosomes from metastatic osteosarcoma cells regulated 215 TAMs signaling to enhance M2 phenotype, thereby eliciting an immunosuppression 216 of tumor-promoting microenvironment by producing TGFB2(Wolf-Dennen et al., 217 2020). As shown in Figure 2, the communication between different types of cells can 218 219 be mediated by exosomes. The aberrant expression of some RNAs in tumor cells affects macrophage function by packaging these RNAs in exosomes. miRNAs in 220 exosomes derived from bladder cancer cells induce macrophage polarization into 221 immunosuppressive phenotype by activating the PTEN/AKT/STAT3/6 pathway(Jiang 222 et al., 2021). miR-21-5p is up-regulated in exosomes of esophageal cancer cells, which 223 converts M0 macrophages into M2 through activation of the PTEN/AKT/STAT6 224 pathway(Song et al., 2021a). cir 0001142 is highly expressed in breast cancer and 225

endoplasmic reticulum stress promotes the release of exosomes encapsulating 226 circ 0001142 in breast cancer cells, which interferes with the process of autophagy 227 228 and polarization of macrophages(Lu et al., 2022). Overexpression of Linc00514 in breast cancer cells enhances the phosphorylation of STAT3 and then activates 229 Jagged1-mediated Notch signaling pathway to accelerates the polarization of co-230 cultured macrophages into M2(Tao et al., 2020). In addition, mutations of genes in 231 tumor cells can result in the changes in macrophage function. The mutation of 232 CREBBP/EP300 in B-lymphoma patient-derived tumor xenografted mice increases 233 M2 polarization of TAMs through FBXW7-NOTCH-CCL2/CSF1 axis(Huang et al., 234 2021c). KRAS is the most frequently mutated oncogene in human neoplasia. 235 Oxidative stress induced KRAS mutation in pancreatic cancer cells and mutated 236 237 KRAS packaged into exosomes are then taken up by macrophages through an AGERdependent mechanism, which causes macrophages switch to an M2-like pro-tumor 238 phenotype via STAT3-dependent fatty acid oxidation(Dai et al., 2020). Macrophages 239 cultured in p53 mutant tumor cell medium reduces M1 markers and inhibit 240 phagocytosis, indicating that p53 mutation facilitates M2 polarization of 241 macrophages(Xu et al., 2022). 242

As displayed in Figure 3, some metabolites such as succinic acid and lactic acid in TME are closely related to the deterioration of tumors(Zhao et al., 2017). The level of succinate and succinic acid receptor (SUCNR1) in the serum of patients with lung cancer is higher than that of healthy people. Mechanically, succinic acid released by cancer cells activates the succinic acid receptor (SUCNR1) signal on macrophages,

248	which is polarized into TAMs through the PI3K- HIF-1 α axis, thus promoting the
249	development of tumors(Wu et al., 2020). Lactic acid, a key metabolite of tumors in
250	TME, is 40 times higher in tumor cells than in normal cells, which is closely associated
251	with the deterioration of tumors. Lactic acid drives tumor progression by inhibiting
252	anti-tumor immunity, increasing tumor angiogenesis and regulating tumor
253	microenvironment(Feng et al., 2017; Végran et al., 2011). Lactic acid in TME is also
254	closely relevant to the function of macrophages. Gastric cancer cell produced lactic
255	acid accelerates M2 polarization of macrophages(Zhang and Li, 2020). Breast cancer
256	derived lactate acid increases macrophage M2 polarization by activating the
257	ERK/STAT3 signaling pathway(Mu et al., 2018) while lactic acid from cancer cells
258	induces M2 polarization by activating Gpr132 in macrophages(Chen et al., 2017). M2
259	polarization of macrophages is facilitated by transitional bladder carcinoma cells
260	secreted lactic acid(Zhao et al., 2015). The abnormal expression of some proteins in
261	tumor cells is also associated with lactate secretion. SLC2A3 overexpression in gastric
262	cancer cells promotes the release of lactic acid, thereby increasing the polarization and
263	infiltration of M2 macrophages(Yao et al., 2020). The expression of some proteins or
264	genes in tumor cells can induce the recruitment and polarization of macrophages by
265	regulating the secretion of chemokines, further promoting the deterioration of tumors
266	(Figure 4). FoxQ1, also known as HFH1, is a member of the forkhead transcription
267	factor family, which is related to the poor prognosis of many tumors. The expression
268	of FoxQ1 in hepatocellular carcinoma cells accelerates the recruitment of macrophage
269	infiltration through CCL2 secretion, which in turn drives hepatocellular carcinoma

metastasis(Xia et al., 2014). The number of TAMs and the volume of tumor decrease 270 in PYK2 knockout mice. Mechanically, PYK2 interferes with the polarization of M2 271 272 macrophages by reducing the expression of NI1ICD, which drives the secretion of CCL2 in breast cancer cells to increase the angiogenesis and tumor-promoting 273 phenotypes in macrophage through IL4R α /pSTAT6 axis. (Muller et al., 2022). The 274 expression of SI-CLP (Stabilin-1 interacting chitinase-like protein) in mouse TS/A 275 cells impedes tumor growth through suppressing the recruitment of macrophages by 276 inhibition of the secretion of CCL2 in breast cancer cells(Yin et al., 2020). The high-277 278 mobility gene group A2 (HMGA2), an oncoprotein, is aberrantly overexpressed in colorectal cancer cells. It is bound directly to STAT3 promoter to activate the 279 transcription, which induces the secretion of CCL2, thereby promoting macrophage 280 281 recruitment(Wang et al., 2022). Overexpression of Spi-B is associated with poor prognosis of patients with lung cancer, which facilitates TAM recruitment by up-282 regulating CCL4 expression(Huang et al., 2021b). The expression of Twist1 in tumor 283 284 cells drives macrophage recruitment and tumor angiogenesis by secreting CCL2(Low-Marchelli et al., 2013). The expression of RKIP is correlated with the expression of 285 CCL5 in breast cancer and the overexpression of RKIP in breast cancer cells inhibits 286 macrophage infiltration to tumor sites through the decrease of CCL5 expression(Datar 287 et al., 2015). The overexpression of BRD4 is associated with poor prognosis in 288 gastrointestinal stromal tumor which enhances the expression of CCL2 in cancer cells 289 by activation of the NF-kB signaling pathway, thereby promoting macrophage 290 recruitment to tumor sites(Mu et al., 2019). Table 2 exhibits the effects of exosomes 291

from tumor cells on macrophage polarization and recruitment.

293 Effects of other cells on polarization of macrophages

The communication between macrophages and other cells in TME also modulates 294 the function of macrophages. In pancreatic ductal adenocarcinoma (PDAC), CAFs 295 induce monocytes to transform into tumor-promoting TAM phenotype by secreting 296 macrophage colony-stimulating factor (M-CSF) and enhancing ROS production in 297 monocytes (Zhang et al., 2017). Mesenchymal stromal cells injected into 298 paracarcinoma could secrete IFN-y, leading to the polarization of macrophages into M1 299 300 phenotype(Relation et al., 2018). Interestingly, salt extracellular environment induces an anti-inflammatory M2 macrophage phenotype(Amara et al., 2016) and higher matrix 301 stiffness strengthens the polarization of M2 macrophages through the integrin β 5-FAK-302 MEK1/2-ERK1/2 pathway(Xing et al., 2021). In addition, supplements of some 303 nutrients can prevent macrophage M2 polarization. Dietary protein or amino acid 304 inhibit M2 polarization of macrophages through ROS/mTOR, thus restoring tumor 305 306 immune response(Orillion et al., 2018). Ocoxin® oral solution (OOS) is a nutritional supplement, which impede M2 protumoral polarization 307 can the of macrophages(Hernandez-SanMiguel et al., 2019). 308

Bacteria regulate polarization of macrophages

310 The function of macrophages is not only affected by various cells in TME, but is 311 also related to microorganisms. Bacterial infection plays a dual role in the development

of cancer. On the one hand, it activates the immune system, which not only has 312 antibacterial effect but also possesses antitumor activity, and the competition of 313 essential nutrients between bacteria and tumor cells in TME also exert anti-tumor 314 effects(Azevedo et al., 2020; Yasunaga and Matsuoka, 2018). On the other hand, 315 bacterial infection can also promote the occurrence of cancer. Globally, 15% of cancers 316 are caused by carcinogenic pathogens, such as HPV infection for cervical cancer, 317 Helicobacter pylori for gastric cancer, Candida albicans for oral squamous cell 318 carcinoma and Streptococcus hemoglobin for bladder cancer(Sawant et al., 2020), 319 320 indicating that the occurrence of tumors can be induced by bacterial infection. Besides, bacterial infection can also affect macrophage polarization. Fusobacterium nucleatum 321 enhances the infiltration and M2 polarization of macrophages by activating CCL20 to 322 323 promote tumor growth(Xu et al., 2021a). Listeria infection drives TAM to exhibit the function of M1 macrophages, with the ability of phagocytic function and tumoricidal 324 activation to exert antitumor effect(Rai et al., 2012). Akkermansia muciniphila impede 325 326 the development of colon cancer by inducing TLR2/NLRP3-mediated M1-like TAM activation(Fan et al., 2021). In addition, some microbial metabolites are also associated 327 with the polarization of macrophages. Pullulan is a non-ionic, non-immunogenic and 328 edible polysaccharide produced by Aureobasidium pullulan. Spermine modified 329 pullulan (PS) activates Akt-, Erk-, and JNK-mediated signaling pathways and NF-KB 330 signaling pathway by up-regulation of TLR1, TLR3, and TLR4, resulting in the 331 polarization of M2 macrophages into M1 phenotype, which alleviates the 332 immunosuppressive TME and restores the function of T cells(Xie et al., 2019). 333

Natural products targeting macrophages in TME

Macrophages are crucial to tumor development and at present, some compounds 335 with the ability of regulating macrophage polarization and recruitment to tumor sites 336 have been found(Saeedifar et al., 2021). Many extracts of traditional Chinese medicine 337 have been reported to have anti-tumor effects, some of which can regulate the 338 polarization of macrophages. KSG-002, an extract of radices Astragalus 339 membranaceus and Angelica gigas with the ratio of 3:1, inhibits macrophage 340 infiltration through increase of NF-kB-mediated TNFa production with no toxicity to 341 rat intestinal epithelial (RIE) cells(Woo et al., 2013). Astragalus mongholicus Bunge-342 *Curcuma aromatica* Salisb. (ARCR) is a typical mixture of medication which can treat 343 a variety of malignancies through impeding M2 polarization of macrophages by 344 regulating the Sp1/ZFAS1/miR-153-3p/CCR5 axis, thereby preventing the 345 development of colon cancer. ARCR at the dose of 6 g/kg/d⁻¹ has no obvious toxicity 346 and adverse reactions in orthotopic transplantation colon cancer model mice (Gu et al., 347 2022; Liu et al., 2022a). The extract of Cordyceps sinensis accelerates M1 polarization 348 of macrophages by activating the NF-kB signaling pathway(Li et al., 2020). Cordyceps 349 sinensis has been considered to be a medicinal plant and health food. However, its long-350 351 term intake may lead to health risks due to the content of As and the related products(Liu et al., 2022b). Some polysaccharides extracted from natural products can also regulate 352 the phenotype of macrophages. Oligo-Fucoidan, a sulfated polysaccharide isolated 353 from the brown seaweed, induces monocyte differentiation into M1-like macrophages 354

and repolarization of M2 macrophages into M1 phenotype(Chen et al., 2020a). G.
lucidum spore polysaccharide (GLSP) increases M1 polarization of macrophages but
does not repress the activity on macrophage growth (Song et al., 2021b). Homogeneous
polyporus polysaccharide facilitates M1 polarization of macrophages of bladder cancer.
But its toxicity is still unclear(Jia et al., 2021).

Chinese medicine formula is characterized by multiple components and multiple 360 targets, some of which have been reported to regulate the polarization of macrophages. 361 Aiduqing formula increases M1 polarization by inhibiting CXCL1 secretion in 362 363 macrophages without noticeable hepatotoxicity, nephrotoxicity, or hematotoxicity observed in vivo (Li et al., 2021). Yu-Ping-Feng (YPF), an ancient Chinese herbal 364 decoction, induces M1 polarization of macrophages by promoting phosphorylation of 365 366 STAT1 but does not affect the osmotic pressure of the medium and the activity of LLC cells and macrophages within 24 h up to the dose of 1 mg/mL (Wang et al., 2019). 367

In addition, some natural compounds isolated from Chinese medicines can also 368 369 affect the development of tumors by regulating macrophages. Astragaloside IV is a natural compound from Chinese herb Radix Astragali and fulfills pleiotropic function 370 in several cancers. It hinders the development of ovarian cancer by inhibiting 371 HMGB1/TLR4 pathway in macrophages with little cytotoxicity within experimental 372 doses (Wang et al., 2021b) and also promotes M1 polarization of macrophages in 373 colorectal cancer without toxicity observed in the test concentration (Liu et al., 2020). 374 Resveratrol isolated from Polygonum cuspidatum increases M1 polarization of 375 macrophages and the ratio of M1/M2(Cheuk et al., 2022). But the low bioavailability 376

is its main limitation, which is extensively metabolized in the liver and intestines 377 (Robertson et al., 2022). In addition, resveratrol analogue HS-1793 induces TAMs 378 379 differentiation into anti-tumor phenotype by enhancement of IFN-y production(Jeong et al., 2014). Dihydroartemisinin (DHA), the active metabolite of artemisinin, is one of 380 381 the most important and effective antimalarial drugs, which is able to regulate various aspects of immune response (Xiao et al., 2022). Dihydroartemisinin increases M1 382 polarization of macrophages in TME of Lewis lung carcinoma via AKT/mTOR 383 pathway without obvious cytotoxicity observed in mice and cells at the experimental 384 385 doses (Xiao et al., 2022) and suppresses M2 polarization by inhibiting STAT3 activation in head and neck squamous cell carcinoma (HNSCC) (Chen et al., 2020b). Natural 386 products associated with macrophage polarization and recruitment are shown in Table 387 388 3.

389 **Discussion**

At present, the treatments of tumors mainly include surgical resection, 390 chemotherapy and radiotherapy, all of which have side effects related to macrophages. 391 Surgical resection removes in situ tumors, but tumor metastasis is the major reason for 392 cancer deterioration. Circulating tumor cells play a key role in tumor metastasis which 393 can combine with TAMs in peripheral blood to promote tumor metastasis(Adams et al., 394 2014; Salmaninejad et al., 2019). As a major cancer treatment, chemotherapy causes 395 many side effects and drug resistance, which is also associated with macrophages. For 396 example, sorafenib, a well-known targeted anti-tumor drug, can promote TAMs 397

infiltration in tumor tissue and further leads to immunosuppressive microenvironment 398 in patients with hepatocellular carcinoma(Zhang et al., 2021b). Radiotherapy can 399 400 directly elicit the death of tumor cells, but also damages immunogenic cells to promote tumor immunity. Moreover, macrophages are also the most radiation-resistant cells, 401 which can produce a large number of antioxidant molecules, thus limiting the effect of 402 radiotherapy(Prenen and Mazzone, 2019). Therefore, targeting macrophages can 403 alleviate some limitations of current tumor treatment, which is expected to become an 404 adjuvant therapy in the future. 405

406 Immunotherapy has become a hot topic in cancer treatment recently and activation of immune system can combat cancer cells(Johdi and Sukor, 2020). 407 Restoration of the normal immune function in TME can enhance the clearance of cancer 408 409 cells without damaging normal cells. Macrophages, as one of the main cells in the immune system, possess the function of clearing antigen. However, macrophages in 410 TME mainly play a role in promoting tumor development due to the influence of the 411 412 surrounding environment. Furthermore, the overexpression of CD47 on the surface of many cancer cells transmit the "don't eat me" signal by interaction with SIRPa protein 413 on macrophages, which inhibits the phagocytosis of macrophages(Chen et al., 2019; 414 Qiu et al., 2018). Therefore, suppressing CD47 expression on tumor cells can promote 415 416 macrophage phagocytosis and hinder tumor deteriorate. There are a large number of macrophages in tumor microenvironment. Once these are transformed into anti-tumor 417 cells, the expression of "don't eat me" signal on tumor cell surface will be inhibited, 418 thus preventing the development of tumors. As displayed in Figure 5, the polarization 419

of macrophages can be regulated by knockout or overexpression of some genes or
proteins in TME, which could provide an idea for tumor treatment by targeting
macrophages. But the adverse effect remains unclear, which needs to be investigated
further.

As mentioned above, some natural products inhibit macrophage polarization and 424 recruitment. However, due to unclear target and off-target toxicity, it is particularly 425 important to design some drug delivery systems improving the targetability and toxicity 426 of compounds. Nanotechnology provides great opportunities for targeted regulation of 427 428 macrophages polarization, which could improve cancer immunotherapy(Ding et al., 2021). Immunostimulation usually starts from the interaction between nanocarriers and 429 innate immune cells such as macrophages(Andon et al., 2017). Therefore, one of the 430 431 most critical issues for nanomedicine to strengthen immunotherapy is the intrinsic effect of drug-free liposomes on activation and polarization of macrophages through 432 cell interaction. The synthesized drug-free mannosylated liposomes enhance anti-tumor 433 434 immunity by inhibiting macrophage polarization from M2 to M1(Ye et al., 2019). Therefore, the preparation of some natural products with definite efficacy into 435 nanomedicine is helpful to improve efficacy and reduce toxicity. Macrophage mannose 436 receptor (MMR or CD206) expressed in TAMs is a key promoter of tumor progression 437 and a major opponent for cancer therapy (De Vlaeminck et al., 2019). Therefore, it is 438 possible to improve the targeting of drugs by designing a vector targeting MMR. 439 Besides, exosomes also play an important role in TME. Can a drug-coating exosome 440 be designed to target macrophages? Bacterial infection can activate the immune system. 441

442 Maybe a vaccine can be designed to activate the immune function in TME, thus443 hindering tumor development.

Macrophages play a prominent role in the development of tumors, and M2 macrophages drive tumor invasion, growth and angiogenesis. Therefore, understanding the factors of affecting macrophage polarization is helpful for subsequent tumor therapy targeting macrophages. The cells in TME induce macrophage polarization by regulating the expression of proteins and genes in macrophages, thus driving the development of tumors, and natural products can reverse the undesired polarization. This review provides new ideas for the development of anti-tumor drugs targeting macrophages.

451 Author contributions

452 HZ and XL contributed to the conception of the manuscript. QPL and YYC wrote

453 the draft. QPL and PA drew the graphs. HZ and KR revised the manuscript.

454 **Declaration of competing interest**

455 The authors have declared that there is no conflict of interests.

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Figure 1 Classification of macrophages. Macrophages can be divided into M1 type and
M2 type. IFN-γ induces the polarization of macrophages into M1 with anti-tumor
activity, while IL-4/IL-13 promotes the polarization of macrophages into M2 with
pro-tumor activity. In addition, M2 macrophages can be subdivided into M2a, M2b,
M2c and M2d under different stimuli. M2a and M2b play an immune regulatory role
and drive Th2 response, M2c inhibits immune response and promotes tissue remodeling,
while M2d facilitates tumor progression.

Figure 2 Effects of exosomes from cancer cells on polarization of macrophages. Cancer cells promote M2 polarization by secreting exosomes to activate several signaling pathways in macrophages.

- 819 Figure 3 Metabolites from cancer cells enhance the polarization of macrophages.
- 820 Succinic acid and lactic acid from tumor cells promote M2 polarization of macrophages.
- Figure 4 Chemokines secreted by cancer cells enhance the recruitment of macrophages.
- 822 Tumor cells secrete a series of cytokines that encourage the recruitment of macrophages
- to the tumor site.
- Figure 5 The regulative mechanism of macrophage M2 polarization.
- 825
- 826 **Table 1** Regulation of macrophage polarization and recruitment
- **Table 2** Effects of tumor cells on macrophage polarization and recruitment
- **Table 3** Natural products and drugs targeting macrophages in TME

Table 1 Regulation of macrophage polarization and recruitment

1 Table 1 Regulation of macrophage polarization and recruitment							
Cancer	Protein	Target	Effect	Model	Refs		
PDA	VentX	-	Promoting phagocytosis of TAMs	In vitro	(Le et al., 2020)		
Breast cancer	integrin b3	PPARc	Promoting M2 polarization	In vivo and in vitro	(Shu et al., 2020)		
Hepatocellular carcinoma	SPON2	SPON2/ α 4 β 1 integrin	Promoting M1 recruitment	In vivo and in vitro	(Zhang et al., 2018b)		
Lung cancer	Prx5	ROS	Inhibiting M2 polarization	In vivo and in vitro	(Seong et al., 2021)		
Colon cancer	MK2	CXCL-12/SDF-1	Promoting angiogenesis	In vivo and in vitro	(Suarez-Lopez et al., 2020)		
Colon cancer	CX3CR1	-	Promoting TAMs apoptosis	In vivo and in vitro	(Zheng et al., 2013)		
Breast cancer	PTEN	CCL2	Inhibiting M2 polarization	In vitro	(Li et al., 2015)		
-	CCL2 and IL-6	caspase-8	Promoting M2 polarization	In vitro	(Roca et al., 2009)		
Breast cancer	OVOL2	IL-10	Inhibiting M2 polarization	In vivo	(Wu et al., 2022)		
Lewis lung cancer	DC-SIGN	-	Promoting M2 polarization	In vitro	(Yan et al., 2016)		
Serous ovarian cancer	ALOX5AP	-	Promoting M2 polarization and recruitment	In vitro	(Ye et al., 2021)		
Colon cancer	ICAM-1	PI3K/AKT	Promoting M2 polarization	In vivo and in vitro	(Yang et al., 2015)		
Renal carcinoma	AIM2	Inflammasome signaling	Enhancing TAMs polarization switch from anti- inflammatory M2 to pro-inflammatory M1	In vivo and in vitro	(Chai et al., 2021)		
Triple-negative breast cancer	SMS2	-	Promoting M2 polarization	In vivo and in vitro	(Deng et al., 2021b)		
Breast cancer	KLF14	RhoA/Rock/STAT3	Inhibiting M2 polarization	In vivo and in vitro	(Chu et al., 2022)		
Colorectal cancer	-	TLR-4/MyD88/NF-κB	prompting M1 polarization	In vivo and in vitro	(Andreuzzi et al., 2022)		
Endometrial cancer	CTHRC1	CTHRC1-integrinβ3-Akt	Promoting M2 recruitment	In vitro	(Li et al., 2019)		
Ovarian Cancer	CTHRC1	STAT6	Promoting M2 polarization	In vitro	(Bai et al., 2020)		
Colon cancer	C5aR	NF-Kb	Promoting M2 polarization and infiltration	In vivo and in vitro	(Piao et al., 2018)		

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Table 2 Effects of tumor cells on macrophage polarization and recruitment	

Cancer	Exosome	Target	Effect	Model	Refs
Breast cancer	Gpr132	-	Promoting M2 polarization	In vivo and in vitro	(Chen et al., 2017)
Gastric cancer	SLC2A3	-	Promoting M2 polarization and infiltration	In vivo and in vitro	(Yao et al., 2020)
Breast cancer	miR-375	SREBP2	Regulating metabolism of macrophages	In vivo and in vitro	(Frank et al., 2021)
Gallbladder cancer	Leptin	STAT3	Promoting M2 polarization	In vitro	(Zhao et al., 2022b)
Breast cancer	Leptin	Ob/ObR	Promoting recruitment of TAMs	In vivo and in vitro	(Gelsomino et al., 2020)
Bladder cancer	miRNA	PTEN/AKT/STAT3/6	Inducing macrophage polarization into immunosuppressive phenotype	In vivo and in vitro	(Jiang et al., 2021)
Esophageal cancer	miR-21-5p	PTEN/AKT/STAT6	Promoting M2 polarization	In vitro	(Song et al., 2021a)
Breast cancer	circ_0001142	circ_0001142/miR-361– 3p/PIK3CB	Promoting M2 polarization	In vitro	(Lu et al., 2022)
Breast cancer	Linc00514	NOTCH	Promoting M2 polarization	<i>In vivo</i> and <i>in vitro</i>	(Tao et al., 2020)
Hepatocellular carcinoma	FoxQ1	VersicanV1/CCL2	Promoting recruitment of macrophages	In vivo and in vitro	(Xia et al., 2014)
Breast cancer	PYK2	Notch1	Regulating monocyte recruitment, macrophage polarization and tumor angiogenesis	In vivo and in vitro	(Muller et al., 2022)
Breast cancer	SI-CLP	-	Inhibiting recruitment of macrophages	In vivo and in vitro	(Yin et al., 2020)
Lung cancer	Spi-B	-	Promoting TAM recruitment to TEM	In vivo and in vitro	(Huang et al., 2021b)
Colorectal cancer	HMGA2	STAT3	Promoting recruitment of macrophages	In vivo and in vitro	(Wang et al., 2022)

Breast cancer	Twist1	-	Promoting recruitment of macrophages	In vivo and in vitro	(Low-Marchelli et al., 2013)	
Breast cancer	RKIP	-	Inhibiting macrophage infiltration into tumor site	In vivo and in vitro	<i>in</i> (Datar et al., 2015)	
Triple-negative breast cancer	RKIP	-	Inhibiting TAMs infiltration into tumor site	In vivo and in vitro	(Frankenberger et al., 2015)	
Nasopharyngeal carcinoma	ISG15	LFA-1-SRC-CCL18	Promoting M2 polarization	In vitro	(Chen et al., 2020c)	
Gastrointestinal stromal tumor	BRD4	NF-κB	Promoting recruitment of M2 macrophages	In vitro	(Mu et al., 2019)	
Breast cancer	CITED2	-	Promoting recruitment of macrophages	In vivo and in vitro	(Jayaraman et al., 2018)	
Glioblastoma	FGL2	CD16/SyK/PI3K/HIF1a	Inducing macrophages to secrete chemokines	In vitro	(Yan et al., 2021)	
Colorectal cancer	SPON2	SPON2/integrin β 1/PYK2	Promoting TAMs infiltration and M2 polarization	In vivo and in vitro	(Huang et al., 2021a)	
DLBCL	CREBBP/EP300	FBXW7-NOTCH- CCL2/CSF1	Promoting M2 polarization	In vivo and in vitro	(Huang et al., 2021c)	
PDA	KRAS	Ferroptosis	Promoting M2 polarization	In vitro	(Dai et al., 2020)	
Lung cancer	p53	-	Promoting M2 polarization	In vivo and in vitro	(Xu et al., 2022a)	
Breast cancer	Annexin 1	FPR2	Promoting M2 polarization	In vivo and in vitro	(Moraes et al., 2017)	
Lewis lung cancer	TNFSF15	STAT1, STAT3 and STAT6	Promoting M1 infiltration and polarization	In vivo and in vitro	(Zhao et al., 2022a)	
Hemangiosarcoma	-	-	Promoting M2 polarization	In vivo and in vitro	(Gulay et al., 2022)	
Gastric cancer	PINK1	-	Promoting M2 polarization	In vivo and in vitro	(Xu et al., 2022b)	
-	PAI-1	p38MAPK and NF-kB	Promoting M2 polarization	In vivo and in vitro	(Kubala et al., 2018)	

Melanoma	Osteopontin	ERK and p38	Promoting macrophage infiltration	<i>In vivo</i> and <i>in vitro</i>	(Kale et al., 2014)
esophageal squamous cell carcinoma	TDO2	AKT/GSK3b/IL-8	Promoting M2 polarization and recruitment	In vivo and in vitro	(Zhao et al., 2021)
Nasopharyngeal carcinoma	MIF	-	Inhibiting ferroptosis of macrophages	In vivo and in vitro	(Chen et al., 2021)
Glioblastoma	MSI1	-	Promoting M2 polarization	In vivo and in vitro	(Yang et al., 2021b)
Lung cancer	succinic acid	PI3K/HIF-1a	Promoting polarization of macrophages to TAMs	<i>In vivo</i> and <i>in vitro</i>	(Wu et al., 2020b)
Melanoma	SCOD	-	Promoting M1 polarization of TAMs	<i>In vivo</i> and <i>in vitro</i>	(Sun et al., 2022)
Glioblastoma multiforme	FX	ERK1/2 and AKT	Promoting macrophages recruitment and M2 polarization	In vivo and in vitro	(Zhang et al., 2020)
Pancreatic cancer	ANXA1	-	Promoting M2 polarization	In vivo and in vitro	(Novizio et al., 2021)
Breast cancer	Fra-1	-	Promoting differentiation of macrophages into M2d	In vitro	(Wang et al., 2010)
Lung cancer	IL1RL10	Rab37/ST2	Enhancing ratio of M1/M2	In vitro	(Tzeng et al., 2018)
Esophageal squamous cell carcinoma	PTEN	PI3K/AKT	Inducing M2 polarization	In vitro	(Yang et al., 2021a)
Melanoma	bcl-2	-	Promoting M2 polarization	In vivo and in vitro	(Di Martile et al., 2020)
esophageal squamous cell carcinoma	FOXO1	FAK/PI3K/AKT	Promoting M2 polarization	In vivo and in vitro	(Wang et al., 2020)
PDA	DCLK1	-	Promoting M2 polarization	In vivo and in vitro	(Chandrakesan et al., 2020)
Breast cancer	TFEB	STAT3	Promoting M2 polarization	In vivo and in vitro	(Fang et al., 2017)
Ovarian cancer	glutamine	-	Promoting M2 polarization	In vitro	(Menga et al., 2021)

	synthetase				
Breast cancer	SNAIL1	-	Regulating macrophage polarization	In vivo and in vitro	(Brenot et al., 2018)
esophageal squamous carcinoma	S100A7	Promoting M2 polarization and recruitment of macrophages to tumor sites		In vivo and in vitro	(Lu et al., 2021)
Breast cancer	Kindlin-2	-	Promoting recruitment of macrophages	In vivo and in vitro	(Sossey-Alaoui et al., 2017)
Non-small cell lung cancer	Angptl2	-	Inducing M2 polarization	In vivo and in vitro	(Wei et al., 2017)
Ovarian Cancer	-	PPA Rγ/NF-κB	Promoting M2 polarization	In vitro	(Deng et al., 2015)
DLBCL	GP130	STAT3	Promoting M2 polarization	In vitro	(Ling et al., 2022)
Non-small cell lung cancer	LAMC2	-	Promoting macrophage infiltration	In vitro	(Liu et al., 2021)
Breast cancer	Oncostatin M	mTORC2-Akt1 -	Promoting M2 polarization	In vivo and in vitro	(Shrivastava et al., 2019)
-	Nodal	-	Promoting M2 polarization	In vitro	(Wang et al., 2014)

Table 3 Natural products targeting macrophages in TME

Name	Cancer	Nature	Target	Effect	Model	Dose	Refs
KSG-002	Breast cancer	Extract	NF-κB/ TNFα	Inhibiting M2 polarization	In vivo and in vitro	500 mg/kg/day in mice; 50, 100, 200, 500 μg/mL in cells	(Woo et al., 2013)
Taraxacum mongolicum	Triple-negative breast cancer	Extract	STAT3 and PD-L1	Inhibiting M2 polarization	In vitro	20, 40, 80 µg/mL	(Deng et al., 2021a)
EAT	Lung cancer	Extract	-	Inhibiting M2 polarization	In vitro	50, 100, 200 μg/mL	(Park, 2019)
ARCR	Colorectal cancer	Extract	Sp1/ZFAS1/miR- 153-3p/CCR5	Inhibiting M2 polarization	In vivo and in vitro	0.64 g/kg/day in cells; 6 g crude drug/kg/day in mice	(Gu et al., 2022)
Huaier extract	Breast cancer	Extract	-	Inhibiting M2 polarization and recruitment of macrophages	In vivo and in vitro	4, 8 mg/mL in cells; 75 mg per mouse	(Li et al., 2016)
Cordyceps sinensis	Triple-negative breast cancer	Extract	NF-κB	Promoting M1 polarization	In vivo and in vitro	100, 200 mg/kg in mice; 0.1, 0.4 mg/mL in cells	(Li et al., 2020)
MEMA	-	Extract	STAT6 and STAT3	Inhibiting M2 polarization and recruitment of macrophages	In vitro	25, 50, 10 μg/mL	(Park et al., 2020b)
GLSP	Hepatocellular carcinoma	Polysacchari de	-	Promoting M1 polarization	In vitro	200, 400, 800 µg/mL	(Song et al., 2021b)
Oligo- Fucoidan	Colon cancer	Polysacchari de	-	Promoting M1 polarization	In vivo and in vitro	150 mg/kg in mice; 400 μg/mL in cells	(Chen et al., 2020a)
Aiduqing	Breast cancer	Formula	CXCL1	Promoting polarization of M2 into M1	In vivo and in vitro	0.7, 1.4 g/kg/day in mice; 20, 40, 80, 100, 200 μg/mL in cells	(Li et al., 2021)
Yu-Ping- Feng	Lewis lung cancer	Decoction	STAT1	Promoting M1 polarization	In vivo and in vitro	117 mg per mouse; 0.125, 0.25, 0.5, 1 mg/mL in cells	(Wang et al., 2019)
β-carotene	Colon cancer	Compound	IL-6/STAT3	Inhibiting M2 polarization	In vivo and in vitro	40 μ M in cells; 5, 15 mg/kg in mice	(Lee et al., 2020)
Astragalosid e IV	Ovarian cancer	Compound	HMGB1/TLR4	Inhibiting M2 polarization	In vitro	10 µg/mL	(Wang et al., 2021b)
Astragalosid	Colorectal cancer	Compound	-	Promoting M1 polarization	In vivo and in	15 mg/kg in mice; 10, 50, 100	(Liu et al., 2020)

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e IV						vitro	nM in cells	
Berberine	DLBCL		Compound	c-myc	Promoting macrophage phagocytosis	In vivo and in vitro	100 mg/kg in mice; 15, 30, 60 μM in cells	(Ren et al., 2021)
Xanthoangel ol	gel osteosarcoma		Compound	STAT	Inhibiting M2 polarization	In vivo and in vitro	25 and 50 mg/kg in mice; 5, 10, 25, 50 μM in cells	(Sumiyoshi et al., 2015)
4- hydroxyderr icin	err osteosarcoma		Compound	-	Inhibiting macrophage activation	In vivo and in vitro	25, 50 mg/kg in mice; 5, 10, 25, 50 μM in cells	(Sumiyoshi et al., 2015)
Resveratrol	Breast cancer		Compound	IL-6/STAT3	Promoting M1 polarization	In vitro	$40 \text{ mg/kg in mice; } 5, 10, 25 \mu\text{M}$ in cells	(Cheuk et al., 2022)
Resveratrol analog	Breast cancer		Compound analog	-	Promoting TAM differentiation into antitumor phenotype	In vivo and in vitro	1.5 mg/kg in mice; 1.25, 2.5, 5 μ M in cells	(Jeong et al., 2014)
Polyporus polysacchari de	Bladder cancer		Polysacchari de	-	Inhibiting M2 polarization	In vitro	1, 10, 100 μg/mL	(Jia et al., 2021a)
Cucurbitacin B	Colorectal cancer		Compound	JAK-2/STAT3	Inhibiting M2 polarization	In vivo and in vitro	0.5, 1 mg/kg in mice; 0.4, 0.8 μ M in cells	(Zhang et al., 2022)
Curcumin	Lung cancer		Compound	p53	Promoting M1 polarization	In vivo and in vitro	5, 10, 20 μM	(Xu et al., 2022a)
Dihydroarte misinin	HNSCC		Compound	STAT3	Inhibiting M2 polarization	In vitro	50 µM	(Chen et al., 2020b)
Dihydroarte misinin	Lewis carcinoma	Lung	Compound	AKT/mTOR	Promoting M1 polarization	In vivo and in vitro	12.5 mg/kg in mice; 0.5 ,1,5 ,10 μ M in cells	(Xiao et al., 2022)
Luteolin	Lewis carcinoma	lung	Compound	-	Inhibiting secretion in TAMs	In vitro	1, 5, 10 μΜ	(Choi et al., 2016)
Epigallocate chin gallate \	Breast cancer	r	Compound	miR-16	Inhibiting macrophage infiltration and M2 polarization	In vivo and in vitro	10 mg/kg in mice; 100 μM in cells	(Jang et al., 2013)
Lupeol	Lewis carcinoma	lung	ung Compound	-	Inhibiting M2 polarization and recruitment of macrophages	In vitro	10, 20, 50, 100 µM	(Park et al., 2020a)
2- methylpyridi ne-1-ium-1- sulfonate	Colorectal cancer		Compound	-	Promoting M1 polarization	In vitro	2, 4, 6 µM	(Rastegari-Pouyani et al., 2022)
Triptolide	Ovarian cancer		Compound	PI3K/Akt/NF-kB	Inhibiting M2 polarization	In vivo and in	0.15 mg/kg/d in mice; 6.25,	(Le et al., 2021)

					vitro	12.5, 25, 50, 100 nM in cells			
Corosolic acid	-	Compound	STAT3	Inhibiting M2 polarization	In vivo and in vitro	17.5 mg/kg in mice; 10, 20, 30 μ M in cells	(Fujiwara 2014)	et	al.,
Oleanolic acid	-	Compound	STAT3	Inhibiting M2 polarization	In vitro	10, 20, 30 µM in cells	(Fujiwara 2014)	et	al.,
Ovatodiolide	Bladder cancer	Compound	-	Reducing expression of tumor promoting factors in TAM exosomes and inhibiting M2 polarization	In vivo and in vitro	5 mg/kg in mice	(Wu et al., 20)		.)
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