



Oral Adjuvant Therapy for Colorectal Cancer: Recent Developments and Future Targets

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1 Oral Adjuvant Therapy for Colorectal Cancer: Recent Developments and Future Targets

2 3 **Abstract:**

4 Colorectal cancer (CRC) is considered the third most frequent malignant neoplasm occurring in
5 both men and women worldwide. Most approaches that have been used to fight and treat this
6 type of malignancy are either invasive or non-selective. Non-invasive therapy using oral route
7 can increase patient compliance and reduce treatment costs. Innovative measures such as use of
8 nanotechnology and theranostic systems have been initiated in the oral therapy, which has been
9 proven to be greatly advantageous in decreasing side effects, improving detection and diagnoses.
10 This manuscript investigates recent innovative and novel therapeutic approaches through oral
11 route and potential targets in the treatment of CRC.

12 **Keywords:** Colorectal cancer, targeted therapy, nanotechnology, oral chemotherapy,
13 immunotherapy, monoclonal antibodies, theranostic systems

14 **1. Introduction**

15 Cells in our body receive different information signals and process them, these signals may allow
16 them to either grow, divide, differentiate or undergo apoptosis. However, when these signals
17 reaching the cells are not followed and get out of control, then these cells become known as
18 cancer cells. Cancer cells are cells that keep on growing, replicating and spreading although they
19 are located near non-stimulated cells [1].

20 There are more than one hundred different types of cancer which are unique from one another by
21 their behavior and response to treatment [2]. Cancer incidents and mortality rates are keep on
22 increasing globally. It was estimated that in 2018 the new cancer incidents will increase up to
23 18.1 million in addition to that the death rates are predicted to reach up to 9.6 million [3]. Among
24 different types of cancer, CRC is ranked as a third common cancer occurring in both genders
25 worldwide. In addition to that, it is second cancer leading to mortality after lung cancer in both
26 men and women according to the 2018 cancer statistics [3]. **According to recent statistics
27 conducted in 2019 for the ten leading cancer types for the estimated new cancer cases and deaths
28 by sex in the United States, CRC ranked 3rd in terms of deaths and incidents after prostate and
29 lung cancer in males, and breast and lung cancer in females. The statistics show that there are**

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2
3 30 about 78,500 new estimated cases and 27,640 estimated deaths in males. On the other hand, there
4
5 31 are 67,100 new estimated cases and 23,380 estimated deaths in females [4].
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7 32 CRC is caused by the abnormal division of cells taking place in rectum as well as in colon
8
9 33 region. The earliest phase of CRC starts with the appearance of clusters of enlarged crypts that
10
11 34 proliferate abnormally, known as polyps. The majority of CRCs develop from abnormal polyps
12
13 35 that later become malignant due to the infiltration to the submucosa [5]. CRCs have many
14
15 36 symptoms associated with it, the main symptoms include rectal bleeding, diarrhea or constipation
16
17 37 which are better known as changing bowel habits, and other symptoms include weight loss,
18
19 38 abdominal discomfort and anemia [6]. There are number of risk factors associated with CRC.
20
21 39 The CRC is more likely in people who had inflammatory bowel diseases and family history of
22
23 40 CRC since the factors disposing CRC such as Lynch Syndrome is caused by a germline mutation
24
25 41 in MMR gene [7]. Approximately half of the families that had Lynch Syndrome carry germline
26
27 42 mutation in MMR genes. Diseases and gut flora disturbance are also predisposing factors to CRC
28
29 43 as the disturbance in the microbiota is able to induce diseases such as IBD or cancers. The
30
31 44 following bacteria were found to impact cancer development such as *Escherichia coli*
32
33 45 *Helicobacter pylori*, *Enterococcus faecalis*, *Clostridium septicum*, *Streptococcus*
34
35 46 *bovis*, *Fusobacterium* spp., and *Bacteroides fragilis* [8]. Sedentary lifestyle, smoking, age,
36
37 47 increased BMI, poor diet that lacks vegetables and fruits while being high in red meat were also
38
39 48 major risk factors associated with the disease [9,10].
40

41 49 Luckily, nowadays there are various approaches to treatment options available for CRC such as
42
43 50 surgery, chemotherapy, radiotherapy and targeted therapies. However, these treatment options
44
45 51 differ depending on the stage of CRC (Table 1). The most common treatment for CRC is usually
46
47 52 surgery or chemotherapy, most of the patients of the metastatic phase or CRC are candidates for
48
49 53 systemic chemotherapy to increase the quality of life and decrease the symptoms [11]. **Currently**
50
51 54 **available adjuvant therapies are depicted in Figure 1.**
52

53 55 Intravenous (IV) 5-Fluorouracil (5-FU) is the main drug of choice used for CRC. Moreover, new
54
55 56 advances in the field of oncology have been developed [12] and recently scientists have
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57 57 introduced new treatment methods such as laparoscopic surgery, resection of metastatic disease,
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59 58 neoadjuvant and palliative chemotherapy. Nevertheless, long-term survival and cure rates were
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61 59 found to give only minimal results [13].
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3 60 Although IV route is most commonly used, patients were seen to prefer oral chemotherapy in
4
5 61 comparison to IV chemotherapy that was observed in the study which was comparing patient
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7 62 preference between oral UFT versus IV 5-FU and leucovorin [14]. The patient choice was
8
9 63 influenced by compliance and drug toxicity. That being said, patients try to avoid traditional
10
11 64 invasive therapy and that was a factor that spiked the scientists' interest to develop new drug
12
13 65 delivery systems that can be given to the patient orally as an oral cancer treatment is having
14
15 66 many advantages such as patient compliance and acceptance as well as cost saving [15].

16
17 67 Innovative measures have been initiated with the oral therapy as there were previous limitations
18
19 68 with the bioavailability primarily because of cytochrome P450 (CYP) activity and drug
20
21 69 transporters, such as P-glycoprotein (P-gp) in gut wall and liver [16]. The use specific, low-
22
23 70 toxicity inhibitors of CYP3A4, (P-gp), and other drug metabolizing enzymes such as
24
25 71 dihydropyrimidine dehydrogenase was initiated as a solution to this problem that lead to the
26
27 72 success of the oral chemotherapy formulations [17]. Other notable innovations that helped oral
28
29 73 cancer therapy was the use of nanotechnology and advanced targeted drug delivery systems [18]
30
31 74 that were either encapsulating chemotherapeutic drugs [19] or being coated with cell surface
32
33 75 specific antigens such as monoclonal antibodies [20]. Theranostic nanomedicine is a recent
34
35 76 technology to fight against cancers in addition to providing diagnoses and scanning applications
36
37 77 as an all in one treatment. This system includes nanoshells, plasmonicnanobubbles, quantum dots
38
39 78 etc. Such new advances in nanoimaging and nanotherapy open doors to the development of
40
41 79 effective cancer treatment [21].

42
43 80 The purpose of this review is to provide the reader with complete up-to-date information related
44
45 81 to oral adjuvant therapy options that are available for CRC. This review further examines
46
47 82 innovative measures such as use of nanotechnology and theranostic systems along with an
48
49 83 overview of potential targets in the treatment of CRC.

46 47 84 **Oral Route of Administration**

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49 85 **Currently, the adjuvant therapy of colorectal cancer mostly requires IV administration,**
50
51 86 **necessitates regular visits to clinics. IV route of administration further leads to discomfort,**
52
53 87 **infection and chances of extravasation. Oral route of administration offers significant advantages**
54
55 88 **like flexibility in the design of dosage form, ease of manufacturing with least sterility constraints,**
56
57 89 **patient convenience, self-administration, cost-effectiveness. However, oral bioavailability of**

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3 90 many anticancer drugs are low and highly variable, low solubility and low permeability,
4 91 instability, and metabolism by intestinal and hepatic enzymes. Therefore, only few oral therapies
5 92 are available in market and are presented in **Table 2**.

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8
9 93 After oral administration, there are two main pathways through which drug act on colon cancer
10 94 as depicted in **Figure 2**. The first pathway follow absorption of drugs into systemic circulation,
11 95 while second pathway allows local targeting to colon site. Several strategies for enhancing oral
12 96 bioavailability are being pursued including the development of pro-drugs, the co-administration
13 97 of inhibitors of enzyme and transporter activity, and various formulation approaches, such as
14 98 excipient enhancement, and polymeric- and lipid-based nanocarriers that deliver the medicine
15 99 through the lymphatic system. Local delivery at colonic site such as prodrugs, covalent linkage
16 100 of a drug with a carrier, pressure dependent systems, pH-sensitive systems, timed released
17 101 systems, microbially triggered systems, bioadhesive systems, osmotic controlled drug delivery
18 102 systems can also be utilized to deliver high drug payload to the colonic site. The benefit of this
19 103 approach can be demonstrated by the fact if 5-FU delivered specifically to the colon, its
20 104 distribution and thus side effects to other organs and tissues can be minimized. In addition, 5-FU
21 105 get converted to active metabolite 5-fluoro-2'-deoxyuridine by the colon tumor, the benefits of
22 106 the 5-FU therapy can be maximized [22]. Therefore, this approach for local colon delivery for
23 107 colon cancer is well investigated and very well reviewed [23] and hence are not discussed
24 108 further.

109 **Capecitabine**

110 An oral fluoropyrimidine drug that has been developed, it acts as a prodrug of 5-FU and is
111 absorbed intact from the intestine which later undergoes a series of conversions until it yields
112 Doxifluridine that gets converted to 5-FU. Capecitabine showed better results than 5-FU as it
113 was showed to elevate the levels of 5-FU up to three times in the tumor as compared to healthy
114 tissue after its administration to cancer patients [24].

115 A randomized phase III study was conducted by Hoff PM et al. to compare capecitabine with
116 bolus 5FU/LV treatment regimen. It was found the tumor response rate to be significantly higher
117 in the capecitabine group (24.8%) than in the 5-FU/LV group (15.5%; P =.005). In addition to
118 that capecitabine produced significantly lower incidence of diarrhea, stomatitis, nausea, and
119 alopecia, as well as grade 3/4 stomatitis and grade 3/4 neutropenia thus significantly less

1
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3 120 neutropenic fever/sepsis. However, only grade 3 hand-foot syndrome and grade 3/4
4 121 hyperbilirubinemia toxicities were more frequent in capecitabine than with 5-FU/LV treatment
5
6 122 [25].
7

9 123 **Oral Irinotecan (CPT-11)**

10
11 124 Irinotecan is a topoisomerase inhibitor [26], that is usually given via IV route to treat cancer,
12
13 125 recent studies and clinical trials are testing irinotecan when given via oral route. One of these
14
15 126 studies showed a phase I dose-escalation trial of irinotecan being administered orally by mixing
16
17 127 CPT-11 IV solution with cran-grape juice to measure its maximum tolerated dose and its dose-
18
19 128 limiting toxicities in cancer patients with solid tumors. The results have shown Grade 4 delayed
20
21 129 diarrhea was the dose-limiting toxicities at the 80 mg/m²/d dosage in patients younger than 65
22
23 130 years of age and at the 66 mg/m²/d dosage in patients 65 or older. As neutropenia was found to
24
25 131 be the major toxicity of oral irinotecan and one patient with previously treated CRC and liver
26
27 132 metastases succeeded in getting a partial response. The findings have led to the conclusion that
28
29 133 dose-limiting toxicities of diarrhea are similar to that observed with IV administration of CPT-
30
31 134 11, as well as the need for further clinical development [27].

31
32 135 Another phase I oral irinotecan study was made by giving it daily for 14 days every 3 weeks in
33
34 136 45 patients with solid tumors to study its pharmacokinetic profile. This time the drug was given
35
36 137 via oral route in a powder-filled capsule at doses ranging from 7.5 to 40 mg/m² per day. The
37
38 138 dose-limiting toxicities found were grade 3 nausea, grade 3/4 vomiting and diarrhea as well as
39
40 139 one occurrence of grade 3 asthenia, as for the maximum tolerated dose it was found at 30 mg/m²
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42 140 per day, and two partial responses were documented [28].

42 141 **Oxaliplatin**

43
44 142 New studies that are aiming to transfer chemotherapeutic agents to oral treatments have
45
46 143 developed Oxaliplatin as an oral formulation to be tested against CRC. This preparation method
47
48 144 included the encapsulation of the chemotherapeutic agent in pH-sensitive alginate microsphere
49
50 145 that has been coated with the mucoadhesive chitosan. The aim behind such formulation was to
51
52 146 protect the drug and make sure that it gets released after passing the acidic GIT media thus
53
54 147 targeting the intestines. This formulation was studied on an orthotopic mouse model of CRC and
55
56 148 was able to reduce the tumor in addition to the mortality[29]. In another study, scientists test the

1
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3 149 synergistic activity of combining the oral formulation of TAS-102 (Lonsurf) along with
4
5 150 intravenous Oxaliplatin against colorectal and gastric cancer cells using a mouse model. TAS-
6
7 151 102 (Lonsurf) is a new antitumor agent that consists of trifluridine (FTD) along with tipiracil
8
9 152 hydrochloride, a thymidine phosphorylase inhibitor approved to be used in the treatment of CRC
10
11 153 that is either unresectable advanced or recurrent. Results have shown that the tumor growth-
12
13 154 inhibitory activity and RTV5 in the animal mouse model given TAS-102 with oxaliplatin were
14
15 155 showing significantly better results than those given monotherapy. Overall the results indicated
16
17 156 that such a synergistic combination give promising results for either CRC or gastric cancer and
18
19 157 can be used against tumors that have not received chemotherapy before as well as those that have
20
21 158 been treated with 5-FU and showed 5-FU resistance [30]. Based on the results of these two
22
23 159 studies, we suggest studying the synergistic effect of oral TAS-102 and oral oxaliplatin on CRC.

24 **160 Nanotechnology and advanced drug delivery systems**

25 161 CRC treatment effectiveness is getting limited recently due to the chemotherapy resistance [31].
26
27 162 This resistance is either intrinsic or acquired and it lowers the effectiveness of the
28
29 163 chemotherapeutic drugs leading to poor patient response, its mechanism is mainly by reducing
30
31 164 drug accumulation and elevating drug export in addition to changing drug targets, and repairing
32
33 165 the DNA damaged by chemotherapy. Other factors include stroma and cancer stem cells [32].
34
35 166 Thus this slow growth in the cancer treatments calls for the need for new therapeutic approaches
36
37 167 such as nanosystems or nanotechnology to solve drug delivery problems[33]. Nanoparticles were
38
39 168 showing great potential for therapeutic molecule protection, transport and loading with various
40
41 169 physiological properties [34–36] as well are targeting and having multiple functions [37,38].
42
43 170 Nanocarrier based drugs which are also known as nanomedicines have shown great benefits in
44
45 171 fighting cancer stem cells (CSC) that were having significant effects on tumor progression and
46
47 172 drug resistance as well as cancer metastasis. These nanomedicines were able to deliver an
48
49 173 adequate amount of the drug to the tumor-targeted cells especially the CSC's niches and this was
50
51 174 not seen in other drug delivery systems since it was considered as a limitation in the conventional
52
53 175 treatment methods [39]. Nanomedicines have shown great therapeutic effectiveness against
54
55 176 pump-mediated drug resistance as well as reducing the harmful effects on normal stem cells due
56
57 177 to its selectivity [40]. The in-vivo mechanisim at which such nano-particles work falls into a
58
59 178 four-step process which includes: the transport through blood circulation to tumor regions via

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3 179 blood vessels; transport across vasculature walls into surrounding tumor tissues; penetrate
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5 180 through the interstitial space to target cells; and cellular uptake by endocytosis and intracellular
6
7 181 delivery. Cellular uptake by endocytosis was found to be achieved through five main different
8
9 182 mechanisms, including phagocytosis, clathrin-mediated endocytosis, caveolin-mediated
10
11 183 endocytosis, clathrin/caveolae-independent endocytosis and micropinocytosis [41].

12
13 184 The newly developed nanomedicine treatments of diseases such as intestinal cancer are showing
14
15 185 promising opportunities in clinical trials [42]. A recent study used a squaline based nanoparticle
16
17 186 filled with cisplatin (SQ-CDDP NP) [43]. The effect of this new formulation was measured by
18
19 187 using a mouse model having intestinal cancer. The results have shown a difference of 10 folds
20
21 188 greater with the new nano-formulation in comparison to un-complexed cisplatin, further
22
23 189 investigation showed that the nano-formulation SQ-CDDP NP stimulated the reactive oxygen
24
25 190 species as well as heavy metal and stress-induced gene expressions and finally apoptosis. **It is**
26
27 191 **also demonstrated that ferulic acid from plant sources can be chemically modified to form**
28
29 192 **poly(ferulic acid) (PFA) to prepare nanoparticles. Both PFA blank and loaded with paclitaxel**
30
31 193 **showed colon tumor inhibition suggesting PFA itself has an anticancer effect in vivo [44] and**
32
33 194 **thus not only enhance drug delivery, but also provide additional anticancer benefits to the**
34
35 195 **patients. Same group also prepared doxorubicin loaded PFA nanoparticles that where shown to**
36
37 196 **released drug continuously under slightly acidic conditions in vitro mimicking the conditions of**
38
39 197 **acidic tumor microenvironments suggested effective drug delivery at tumor site. These**
40
41 198 **nanoparticles showed enhanced permeability and retention at tumor site in vivo while reducing**
42
43 199 **the toxicity of free doxorubicin and improving its safety [45].**

44
45 200 Nanoemulsion systems have been also used in the treatment of CRC, a recent study used a
46
47 201 cisplatin third generation analogue known as oxaplatin that is used as first-line therapy in
48
49 202 combination with 5-FU in the treatment of CRC. Since both drugs have a low bioavailability due
50
51 203 to bad membrane permeability a new invention was needed to increase their efficacy. An ion
52
53 204 pairing complex was created between oxaplatin and a deoxycholic acid derivative to increase
54
55 205 permeability followed by the preparation of water-in-oil-in-water nano-emulsions including
56
57 206 oxaplatin/deoxycholic acid and 5-FU to increase the drug absorption when taken orally. The
58
59 207 study also tested the membrane permeability by using Caco-2 cell monolayer and an artificial
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208 intestinal membrane. Then by using the mouse animal model bioavailability testing and CRC cell

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3 209 growth inhibition was conducted after administering the formulation orally and the results have
4
5 210 shown greater in vivo permeability and a significant increase in oral absorption and
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7 211 bioavailability, as well as better tumor growth inhibition. Thus all these findings gave a better
8
9 212 understanding of the importance of using nanomedicine and its development in treating cancer as
10
11 213 well as using it in oral combination therapies for CRC[46].

12
13 214 Another advanced targeted drug delivery system that has been introduced to be used against
14
15 215 CRC is the use of liposomes when combined with a chemotherapeutic drug. In a recent
16
17 216 study[47], two anti-cancer drugs have been used in the treatment of CRC the first one being
18
19 217 Apatinibmesylate, a new and selective VEGFR-2 inhibitor that can be used to treat a variety of
20
21 218 tumors and the second one being docetaxel (Taxotere), a traditional anticancer drug that is a
22
23 219 semisynthetic taxoid in solid tumors. The drug delivery systems used were a liposome and
24
25 220 methoxypoly(ethylene glycol)-poly(ϵ -caprolactone) (MPEG-PCL) to deliver apatinib (Lipo-Apa)
26
27 221 and docetaxel, correspondingly. The Co-administration of the two systems showed synergistic
28
29 222 effects on stopping the cell proliferation and inducing cell programmed death of CT26 cells in
30
31 223 vitro. Moreover, when the treatment was given to the animal model a significant improvement
32
33 224 was shown in the anti-tumor activity in a subcutaneous xenograft model in addition to the
34
35 225 abdominal metastasis model of CRC. thus leading to the conclusion that these two formulations
36
37 226 have the potential to be used clinically in CRC therapy[47].In another study, liposomes were
38
39 227 conjugated with folic acid enclosing Oxaliplatin a monoclonal antibody and entrapped in alginate
40
41 228 beads coated with Eudragit-S-100 to be administered orally to the animal mouse model have
42
43 229 CRC tumors[48]. The study showed positive results with the ability of these beads to be used as
44
45 230 a potential carrier in CRC.

46
47 231 Furthermore, newer advanced targeting techniques were introduced such as formulating folic
48
49 232 acid conjugated liposomes containing Oxiplatin and entrapping them inside aliginate beads that
50
51 233 were coated with Eudragit-S-100 to achieve effective drug delivery to CRC site [48]. Oral
52
53 234 aliginate microcapsules have also been formulated to successfully deliver curcumin-loaded
54
55 235 micelles to the CRC and promote the concept of chemotherapy at home [49].

56
57 236 Scientists have also succeeded in the development of a targeted large intestinal oral nanoparticle
58
59 237 vaccine that is consisting of pH-dependent microparticles to induce colorectal immunity. This
60
238 study was done on a mouse animal model in order to see the efficacy of such a vaccine in the

239 protection against rectal or vaginal viral changes to the mucosa. The study has also stated the
240 potential application of this new delivery technology to be used in different forms of vaccines
241 such as DNA, recombinant proteins, peptides as well as others. Furthermore, it suggested a new
242 approach to formulate vaccines fighting against mucosal malignancies such as colorectal as well
243 as cervical cancer [50].

244 **Immunotherapy**

245 Immunotherapy treatments function by overcoming or relieving tumour-induced
246 immunosuppression, thereby enabling immune-mediated tumour clearance[51]. Recently cancer
247 immunotherapy has become a validated clinical treatment for various types of cancers. This kind
248 of treatment has many approaches to the cancer treatment such as the use of cancer vaccines,
249 adoptive transfer of *ex vivo* activated T and natural killer cells, oncolytic viruses, and the use of
250 antibodies or recombinant proteins that may co-stimulate cells or cause blockage to the immune
251 checkpoint pathways [52].

252 Angiogenesis has always been a concern with tumor formation and metastasis, thus
253 antiangiogenic treatments are available these days. The use of monoclonal antibodies (mAbs) is
254 promising treatment option and receiving remarkable clinical success for lymphomas and solid
255 tumors [53].

256 A recently developed small-molecule inhibitor of vascular endothelial growth factor receptor-2
257 (VEGFR-2) which is better known as Apatinib has shown to possess oral bioavailability when
258 treating various cancers yet it's still being studied under clinical trials [54]. A recent case report
259 that was published on the use of Apatinib as a third line therapy given to two Chinese patients
260 having metastatic CRC displayed promising benefits after the drug treatment the chance of
261 prolonged survival of mCRC patients along with good safety and tolerability profile. The first
262 patient who was a 52-year-old female achieved progression-free survival period of four months
263 and an overall survival of eleven months however she did not continue the treatment due to
264 abdominal distension and loss of appetite. On the other, hand the second patient who was a 59-
265 year-old man, achieved progression-free survival period of more than ten months later on due to
266 PD is shown on frequent CT scans the drug administration was stopped. This case report
267 suggested further investigation on the drug to be given as a single drug or in combinations, as
268 well as it raised the question of the use of this drug in other ethnic groups due to regional

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3 269 differences. Finally report recommended further research on the mechanisms of drug resistance,
4 270 alternative triggers of angiogenesis, and the potential predictive biomarkers that aid in patient
5
6 271 selection [55].
7

8
9 272 Regorafenib is another orally administered monoclonal antibody that is the first small-molecule
10
11 273 multi-kinase inhibitor used for metastatic CRC. Regorafenib has undergone a phase 3 trial and
12
13 274 showed an overall survival benefit in comparison to the placebo that shows its potential to be
14
15 275 used with patients who didn't respond to standard treatments[56].
16

17 276 **Theranostic Systems and new developments for CRC treatment**

18
19 277 Nowadays researchers are looking for methods to monitor and treat the human body by
20
21 278 noninvasive means. Nanotechnology was the gate to develop a noninvasive detection method
22
23 279 and targeted treatments. The development of such nanoscale products is vital because it will lead
24
25 280 to early detection as well as a prompt localized treatment only to the affected body tissues such
26
27 281 as cancer cells. The idea of a carrier to target, detect and treat a non-healthy cell is better known
28
29 282 as Theranostics. This system combines detection agents used in diagnosis as well as the drugs
30
31 283 used for treatment leading to an all-in-one, localized, diagnostic and treatment system.
32
33 284 Nowadays researchers are studying nano-theranostic systems that use imaging nanoparticles able
34
35 285 to use therapeutic systems [57].
36

37 286 Theranostic nanoparticles were also having the advantage over normal radiation as radiation may
38
39 287 produce some damages to healthy tissue in contrast to the radio-sensitized nanoparticles that only
40
41 288 affect the diseased cells while limiting the dose to healthy organs [58]. A very recent study
42
43 289 conducted was using all in one Theranostic system nano-agent with ROS generation, PDT and
44
45 290 CTD. These researchers have developed a Biocompatible copper ferrite nano-sphere (CFNs) that
46
47 291 was used to intensify the ROS production by laser creating direct electron transfer and photo
48
49 292 enhanced Fenton reaction in addition to increasing the photothermal conversion creating a
50
51 293 synergistic action on the treatment. By using the oxygen generation properties while depleting
52
53 294 the copper ferrite nano-spheres from glutathione they were able to come up with better
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55 295 photodynamic therapy and photodynamic therapy for cancer eradication in general [59].
56

57 296 **Future Perspectives:**

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3 297 The overall goal of adjuvant therapy is patient survival and should be based on toxicity, ease of
4 298 administration, and cost since it is for longer duration generally for 6 months. Therefore, better
5 299 strategies that provides not only improved adjuvants but also that allows self-administration with
6 300 minimum side effects. The oral route offers significant advantages over other routes of
7 301 administration like flexibility in the design of dosage form, ease of manufacturing with least
8 302 sterility constraints, patient convenience, self-administration, cost-effectiveness. However, oral
9 303 bioavailability of many anticancer drugs are low and highly variable, low solubility and low
10 304 permeability, instability, and metabolism by intestinal and hepatic enzymes. Therefore as of now,
11 305 only few drugs have reached the market. Many pharmaceutical approaches have been identified
12 306 for colon drug delivery following oral administration such as prodrugs, covalent linkage of a
13 307 drug with a carrier, pressure dependent systems, pH-sensitive systems, timed released systems,
14 308 microbially triggered systems, bioadhesive systems, osmotic controlled drug delivery systems.
15 309 Nanoparticle formulations such as nanoparticles, nanoemulsions, liposomes are also developed
16 310 to deliver adequate amounts of the drug to the tumor-targeted cells especially the CSC's niches,
17 311 have shown great therapeutic effectiveness against pump-mediated drug resistance as well as
18 312 reducing the harmful effects on normal cells due to its selectivity. In this era of precision
19 313 oncology as more specific and cost effective techniques for molecular profiling of colorectal
20 314 tumors are evolving, more specific adjuvant therapies based on molecular subtypes of colorectal
21 315 tumors will emerge. Advances in bioinformatics and availability of high-throughput gene
22 316 expression and other functional genomics data sets such as Gene Expression Omnibus (GEO)
23 317 database had led to identification of potential biomarkers for the management of CRC [60,61].
24 318 New therapeutic targets including *PD-1/PD-L1* [62], *NEK2* [63], *COL1A1* [63], *BCL9* [64], *miR-*
25 319 *124* [65], *9p21 locus* [66] and many others associated with progression and prognosis of
26 320 colorectal cancers were identified by integrating protein-protein interactions (PPIs) network and
27 321 gene expression data and co-expression analysis. In earlier study, combination of *NEK2* siRNA
28 322 and chemotherapeutic agent cisplatin showed improved antitumor activity in colorectal cancer
29 323 suggesting the benefits of combined treatment using potential therapeutic targets with traditional
30 324 chemotherapeutic agents [67]. In near future, combining these gene targets along with other
31 325 therapies will be a viable approach for treatment of CRC. It is hoped that these innovations,
32 326 particularly those in nanotechnology, will facilitate effective and safe oral chemotherapy at
33 327 home, without introducing further cost for healthcare systems in near future. However,

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3 328 adherence to oral therapy needs to address properly. Overall, authors believe that oral route is a
4
5 329 promising approach especially for colorectal cancer.
6

7 **Executive summary**

8 **Overview on colorectal cancer (CRC)**

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- 10
- 11 • Colorectal Cancer ranks third in terms of deaths and incidents in both genders.
- 12
- 13 • Nowadays there are many treatment options available for CRC such as surgery,
14 chemotherapy, radiotherapy and targeted therapies that differ depending on the stage of the
15 cancer.
- 16
- 17 • Patients prefer oral non-invasive chemotherapy in comparison to IV chemotherapy.
- 18
- 19 • The site of action as well as mode of action of the chemotherapeutic and chemopreventive
20 agents influence the rationale for colon-targeted oral drug delivery.
21
22

23 **Non-invasive treatment approaches for colorectal cancer (CRC)**

- 24
- 25 ○ New studies that are aiming to transfer chemotherapeutic agents to oral treatments to increase
26 patient compliance such as the development of TAS-102 (Lonsurf), Capecitabine (Xeloda),
27 oral irinotecan and Oxiplatin.
- 28
- 29 ○ Since CRC treatments are being limited due to cancer chemo- resistance scientists have
30 started incorporating drugs in nanocarriers such as liposomes to fight resistance and solve
31 drug delivery problems.
- 32
- 33 ○ Recent studies focus on using immunotherapy treatment for CRC as they function by
34 overcoming or relieving tumour-induced immunosuppression, and enable immune-mediated
35 tumour clearance. Regorafenib (Stivarga) is an example of such oral immunotherapy.
- 36
- 37 ○ A new technology that combines detection agents used in diagnosis as well as the drugs used
38 for treatment leading to what's known as an all-in-one, localized, diagnostic and treatment
39 system.
- 40
- 41 ○ In this era of precision oncology as more specific and cost effective techniques for molecular
42 profiling of colorectal tumors are evolving, more specific adjuvant therapies based on
43 molecular subtypes of colorectal tumors will emerge. It is hoped that these innovations,
44 particularly those in nanotechnology, will facilitate effective and safe oral chemotherapy at
45 home, without introducing further cost for healthcare systems.
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Table 1: Different stages of colorectal cancer and their treatment options [68]

Stage	Definition	Treatment Options
Stage 0	Localized; didn't grow beyond the colon inner lining.	Polyps are removed during colonoscopy (also known as polypectomy)
Stage I	Cancer grown deeper through the colon wall layers, however, it has not spread yet.	Removal of affected area through local excision (resection surgery)
Stage II	Cancer grown outside the colon wall and possibly spread to nearby tissue but not yet spread through the lymph nodes. Further divided into 3 types, IIA, IIB and IIC.	Resection surgery with or without adjuvant chemotherapy
Stage III	Cancer spread to close by lymph nodes. Further divided into 3 types, IIIA, IIIB and IIIC.	Surgical resection with adjuvant chemotherapy and other therapies if necessary, Radiation and/or chemotherapy
Stage IV	Cancer spread all over the body and reached the metastatic stage. Further divided into 2 types; IVA and IVB	Surgical resection of colon along with surgical removal of other affected parts of the body, chemotherapy Combinations of chemo and/or targeted therapies before or after surgery, Radiation therapy for symptomatic relief

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Table 2: Oral chemotherapy Drugs used in Colorectal Cancer in the Market

Chemotherapy	Trade name	Class
Capecitabine	Xeloda®	Antineoplastics, Antimetabolite
Regorafenib	Stivarga®	Receptor tyrosine kinase inhibitor
Trifluridine-tipiracil hydrochloride	Lonsurf®	Trifluridine: thymidine-based nucleoside analogues. Tipiracil: thymidine phosphorylase inhibitors.
Tegafur/Uracil	Uracel™	Dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines

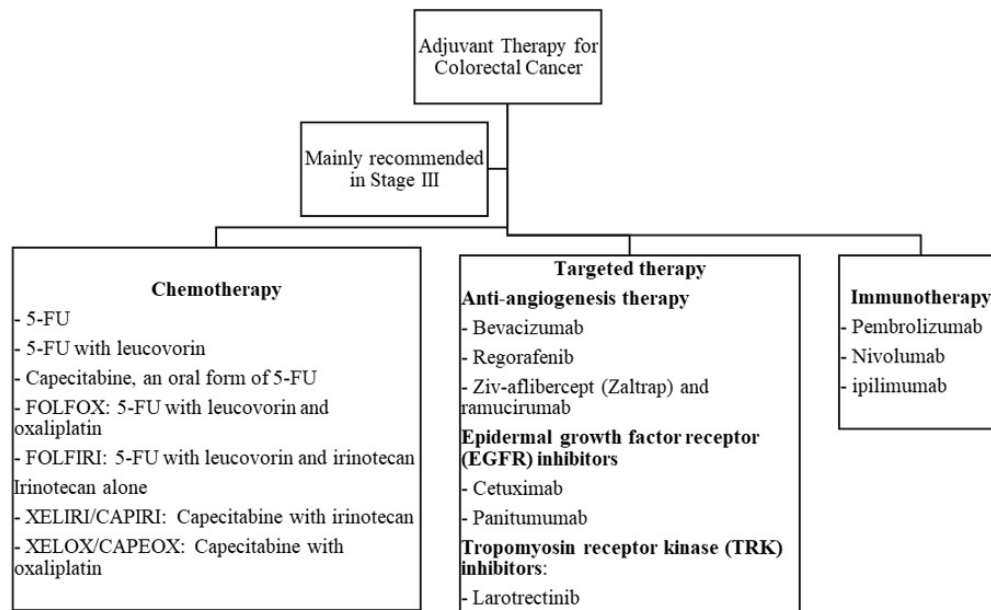


Figure 1: Currently Available Adjuvant Therapy for Colorectal Cancer

241x148mm (96 x 96 DPI)

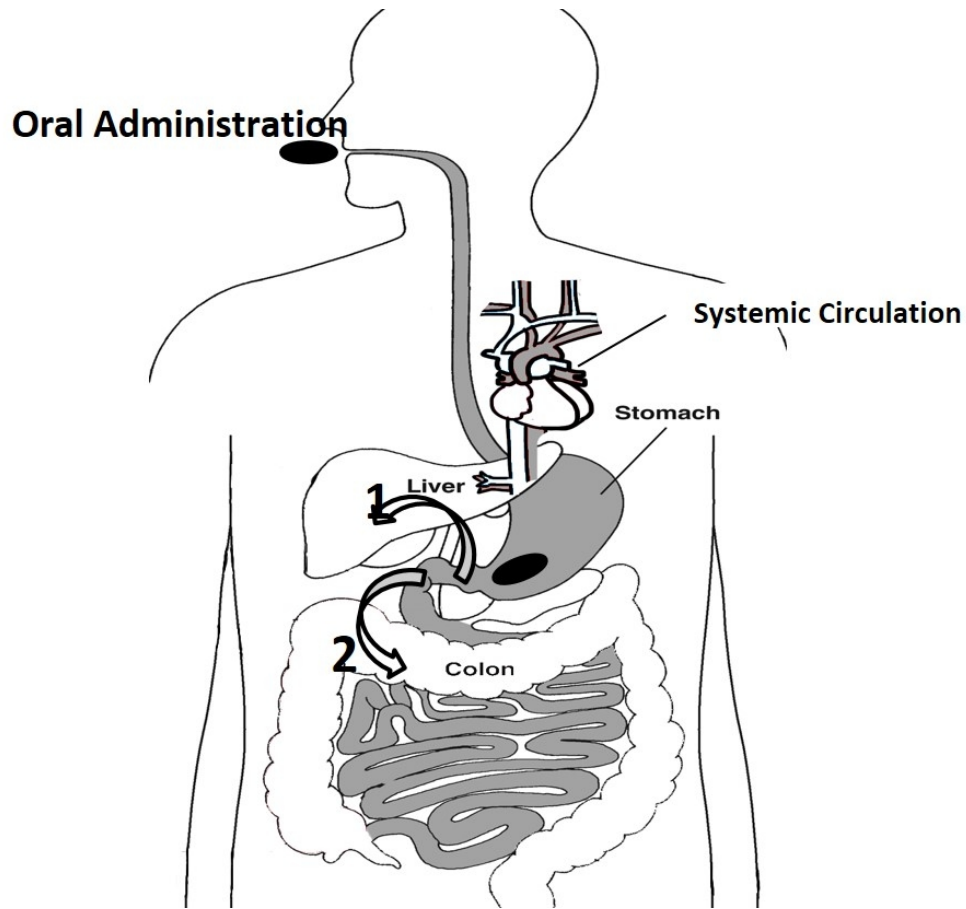


Figure 2: Main pathways through which drug act on colon cancer following oral administration. The first pathway (1) follow absorption of drugs into systemic circulation, while second pathway (2) allows local targeting to colon site

154x139mm (150 x 150 DPI)