| An Emerging Role for Anti-inflammatory Agents |                              |   |    |  |  |
|---|------------------------------|---|----|--|--|
| for   | · Che                        | moprevention.   | 1  |  |  |
| Re  | ferend                       | ces   | 4  |  |  |
|   |                              |   |    |  |  |
| Me  | echan                        | istic Aspects of COX-2 Expression in Colorectal Neoplasia | 7  |  |  |
| 1   | Mole                         | ecular Basis of Colorectal Adenoma and Carcinoma          | 9  |  |  |
|   | 1.1                          | Genetic Basis of Adenoma-Carcinoma Sequence               | 9  |  |  |
|   | 1.2                          | Adenomatous Polyposis Coli                                | 10 |  |  |
|   | 1.3                          | The Microsatellite Instability Pathway in CRC             | 11 |  |  |
|   | 1.4                          | The Epigenetic Pathway in CRC                             | 12 |  |  |
|   | 1.5                          | COX-2/mPGES-1 Pathway                                     | 12 |  |  |
|   | 1.6                          | Prostaglandin Transporters in CRC                         | 16 |  |  |
|   | 1.7                          | Epidermal Growth Factor Receptor Pathway                  | 16 |  |  |
|   | 1.8                          | Peroxisome Proliferator-Activated Receptors.              | 17 |  |  |
|   | 1.9                          | Tumor Microenvironment in Colorectal Carcinogenesis       | 18 |  |  |
| 2   | COX-2 Gene Expression in CRC |   | 18 |  |  |
|   | 2.1                          | Transcriptional Regulation                                | 19 |  |  |
|   | 2.2                          | Post-transcriptional Regulation and the 3'                |    |  |  |
|   |                              | Untranslated Region.                                      | 21 |  |  |
|   | 2.3                          | AU-Rich Elements and ARE-Binding Proteins                 | 22 |  |  |
|   | 2.4                          | MicroRNAs   | 26 |  |  |
| 3   | Con                          | clusions  | 29 |  |  |
| Re  | ferend                       | ces   | 30 |  |  |
|   |                              |   |    |  |  |
| Mo  | ode o                        | f Action of Aspirin as a Chemopreventive Agent            | 39 |  |  |
| 1   | Intro                        | duction   | 41 |  |  |
| 2   | Mec                          | hanisms of Action of Aspirin                              | 42 |  |  |
|   | 2.1                          | Historical Overview of Aspirin and its Mechanism          |    |  |  |
|   |                              | of Action (Box. 1)  | 42 |  |  |
|   | 2.2                          | Insights into the Mechanism of Inhibition                 |    |  |  |
|   |                              | of COXs by Aspirin  | 44 |  |  |
| 3   | Phar                         | macology/Pharmacokinetic of Aspirin                       | 49 |  |  |





|        | 3.1        | COX-Isozyme Selectivity in Vitro                           | 49   |
|--------|------------|--|------|
|        | 3.2        | Pharmacokinetic  | 50   |
|        | 3.3        | Determinants of Achieved COX-Isozyme Selectivity           |      |
|        |            | by Clinical Doses of Aspirin.                              | 52   |
| 4      | Role       | of Platelets in Tumorigenesis                              | 53   |
|        | 4.1        | Platelet-Mediated Mechanisms in Tumorigenesis              |      |
|        |            | and Metastasis.  | 53   |
|        | 4.2        | Role of Platelet COX-1 in Aspirin Chemoprevention          | 56   |
| 5      | COX        | K-Independent Mechanisms of Aspirin Chemoprevention        | 57   |
|        | 5.1        | Inhibition of NF-kB  | 57   |
|        | 5.2        | Interruption of Extracellular Signal-Regulated Kinases     | 59   |
|        | 5.3        | Induction of Apoptosis by Caspase Activation               | 59   |
|        | 5.4        | Inhibition of Wnt/ $\beta$ -Catenin Pathway                | 59   |
| 6      | Aspi       | rin-Mediated Acetylation of Extra-COX Proteins             | 59   |
| 7      | Cond       | clusions   | 60   |
| Re     | ferenc     | es   | 61   |
|        |            |  |      |
| Co     | xibs:      | Pharmacology, Toxicity and Efficacy                        |      |
| in     | Canc       | er Clinical Trials   | 67   |
| 1      | Intro      | duction  | 69   |
| 2      | Phar       | macology of tNSAIDs and Coxibs                             | 76   |
| 3      | Effic      | eacy of Coxibs in CRC Chemoprevention Trials               | 77   |
| 4      | CV '       | Toxicity of Coxibs.  | 80   |
| •      | 41         | Risk Estimates: Data from Trials and Observational Studies | 80   |
|        | 4.2        | Mechanisms of CV Toxicity of Coxibs                        | 83   |
|        | 43         | Ongoing Randomized Clinical Trials with Coxibs/NSAIDs.     | 85   |
| 5      | Con        | clusions and Perspectives                                  | 86   |
| Re     | ferend     |  | 87   |
| ne     | ieiein     |  |      |
| C      | )X.2       | Active Agents in the Chemonrevention                       |      |
| of     | Colo       | rectal Cancer  | 95   |
| Re     | feren      | PS   | 102  |
| ACC.   | Terein     |  |      |
| Ne     | w NS       | SAID Targets and Derivatives for Colorectal                |      |
| Ca     | ncer       | Chemoprevention  | 105  |
| 1      | Intro      | aduction   | 106  |
| 2      | Tara       | eting COX-2  | 109  |
| 2      |            | / Independent Targets                                      | 110  |
| 5      | 31         | Inhibition of cGMP PDFs                                    | 110  |
|        | 3.1<br>3.1 | Generation of Reactive Ovygen Species                      | 112  |
|        | 3.2<br>2.2 | Downregulation of Survivin                                 | 112  |
|        | 5.5<br>2 1 | Other COV Independent Targets                              | -11/ |
| 1      | 3.4<br>Car | olucione   | 114  |
| 4<br>P | Con        |  | 117  |
| ке     | ieren      | Ces  | 11/  |

| As | pirin in Prevention of Sporadic Colorectal Cancer:                |     |  |  |
|----|---|-----|--|--|
| Cu | irrent Clinical Evidence and Overall Balance                      |     |  |  |
| of | Risks and Benefits  | 121 |  |  |
| 1  | Introduction  | 122 |  |  |
| 2  | Aspirin in Prevention of Colorectal Cancer.                       | 122 |  |  |
|    | 2.1 Observational Studies   | 122 |  |  |
|    | 2.2 Randomised Controlled Trials                                  | 125 |  |  |
| 3  | Effects on Other Cancers  | 131 |  |  |
| 4  | Overall Balance of Risk and Benefit                               | 135 |  |  |
| 5  | Summary and Outstanding Issues                                    | 137 |  |  |
| Re | ferences  | 139 |  |  |
| Nu | tritional Agents with Anti-inflammatory Properties in             |     |  |  |
| Ch | emoprevention of Colorectal Neoplasia                             | 143 |  |  |
| 1  | Naturally Occurring Substances Used as Pharmaceutical             |     |  |  |
|    | Preparations—'Nutraceuticals'                                     | 144 |  |  |
| 2  | Anti-inflammatory Agents for Prevention and Treatment of CRC      | 145 |  |  |
| 3  | Anti-inflammatory Nutraceuticals with Evidence                    |     |  |  |
|    | of Anti-CRC Activity  | 145 |  |  |
|    | 3.1 Omega-3 PUFAs   | 145 |  |  |
|    | 3.2 Curcumin  | 149 |  |  |
|    | 3.3 Resveratrol   | 151 |  |  |
|    | 3.4 Other Dietary Polyphenols                                     | 152 |  |  |
|    | 3.5 Other Natural Anti-inflammatory Agents with                   |     |  |  |
|    | CRC Chemopreventative Efficacy                                    | 152 |  |  |
| 4  | Summary   | 153 |  |  |
| Re | ferences  | 153 |  |  |
| ~  |   |     |  |  |
| Ge | enetics, Inheritance and Strategies for Prevention in Populations | 1   |  |  |
| at | High Risk of Colorectal Cancer (CRC)                              | 157 |  |  |
| 1  |   | 159 |  |  |
| 2  | CAPP1   | 163 |  |  |
|    | 2.1 CAPP1 Trial Design  | 164 |  |  |
|    | 2.2 CAPP1 Endpoint Ascertainments.                                | 165 |  |  |
|    | 2.3 CAPP1 Laboratory and Statistical Methods.                     | 165 |  |  |
|    | 2.4 CAPP1 Results   | 166 |  |  |
|    | 2.5 CAPP1 Toxicity  | 168 |  |  |
|    | 2.6 CAPP1 Conclusions   | 169 |  |  |
| 3  | Chemoprevention in Lynch Syndrome: CAPP2                          |     |  |  |
|    | 3.1 CAPP2 Trial Design  | 172 |  |  |
|    | 3.2 CAPP2 Endpoint Ascertainments.                                | 172 |  |  |
|    | 3.3 CAPP2 Statistical Methods                                     | 172 |  |  |
|    | 3.4 CAPP2 Results   | 175 |  |  |
|    | 3.5 CAPP2 Toxicity  | 178 |  |  |
|    | 3.6 CAPP2 Discussion.   | 179 |  |  |

| 4  | CAPP3      | 180 |
|----|------------|-----|
| 5  | Conclusion | 180 |
| Re | ferences   | 181 |